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# Editorial

## INTRAVENOUS ADMINISTRATION OF GELATIN AND HISTOLOGIC CHANGES IN THE KIDNEY

ONE OF the major problems in the development of a plasma substitute has been the elimination of toxic properties inherent in the substitute or produced in its processing. A number of proposed plasma substitutes known to increase the plasma volume such as acacia, pectin, globin and bovine albumin have been abandoned only because of these toxic properties.

In the early years of World War II several gelatins were studied extensively as substitutes for plasma. One of these, a preparation designated as Knox P-20, is the subject of a special report from the National Research Council published in 1944 in *The Journal of the American Medical Association*,[1] which stated that a gelatin of the Knox P-20 type is of optimal value in the treatment of hemorrhage and shock. This report also stated that "many repeated injections in animals have been given without evidence, histologic or clinical, of toxicity or irreversible accumulation."

Knox P-20 gelatin is prepared from the hard bones of cattle and differs in that respect from other gelatins prepared from skins and hides. It is prepared especially for intravenous use in a plant apart from the commercial manufacture of gelatin. Through the combination of its source material and its processing, Knox P-20 is a unique colloid for intravenous use in that it is nontoxic and an adequate replacement for lost plasma volume.

Attention has been directed by several investigators to the differences in gelatins derived from bone and from hides.[2] The ossein gelatin, Knox P-20, is a poorly degraded gelatin which has a predominantly long chain molecular structure which permits relatively slow excretion by the kidney. The gelatin prepared from hides for intravenous use is

From the schools of medicine of the Harrison Department of Surgical Research and the Department of Pathology, University of Pennsylvania.

1. Evaluation of Studies on Gelatin Preparations for Intravenous Use, National Research Council, J. A. M. A. **125**:284 (May 27) 1944.

2. Koop, C. E.: The Use of Specially Prepared Gelatin Solution as a Plasma Substitute, S. Clin. North America **24**:1300-1315 (Dec.) 1944. Memoranda and Reports on Physical Chemical Properties of Gelatin and Other Blood Substitutes, OEMcmr Contracts 139 and 142.

a highly degraded colloid of short chain molecular structure allowing rapid excretion of the gelatin by the kidney.

The short chain gelatins may be excreted in as short a period as twelve hours, while the unmetabolized portion of Knox P-20 may remain in the circulation because of its slower excretion by the kidney for periods up to five days.[3]

The recent publication by Skinsnes [4] relative to the production of nephrosis by a hide gelatin prompted us to review our own histologic material relative to the infusion of Knox P-20 and possible renal damage. We have reported previously a summary of our findings in the dog and in man. Renal function, as determined by urea clearance, was apparently unimpaired after single and repeated infusions of gelatin.[5a]

No evidence of chronic renal damage or of the storage of gelatin was noted in normal dogs given single and repeated gelatin infusions.[5] This impression was confirmed in the study of human autopsy material.[5a] A review of our own histologic material has not altered these conclusions.

Our investigations have shown that Knox P-20 and other gelatins are not associated with histologic changes in the kidney, with changes in renal function or with deleterious reactions even in those with a diminished renal reserve. Lowell and her co-workers [6] found no significant change in urine urea nitrogen in 20 dogs, although there was transient albuminuria for twenty-four hours. "Other tests pertaining to cardiac, hepatic and renal function showed no changes." The only constant finding in histologic studies of the kidneys of mice, rabbits and dogs after infusion with fifteen varieties of bone gelatin was an

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3. (*a*) Koop, C. E.; Fletcher, A. G.; Riegel, C., and Lockwood, J. S.: Gelatin as a Plasma Substitute: A Preliminary Report of Clinical Experience, Surgery **15**:839-858 (May) 1944. (*b*) Koop, C. E.; Riegel, C.; Grigger, R. P., and Barnes, M. T.: A Study of Protein Hydrolysates, Ossein Solution and Glucose in Parenteral Nutrition, Surg., Gynec. & Obst. **84**:1065-1070 (June) 1947.

4. Skinsnes, O. K.: Gelatin Nephrosis: Renal Tissue Changes in Man Resulting from the Intravenous Administration of Gelatin, Surg., Gynec. & Obst. **85**:563-571 (Nov.) 1947.

5. (*a*) Parkins, W. M.; Koop, C. E.; Riegel, C.; Vars, H. M., and Lockwood, J. S.: Gelatin as a Plasma Substitute, with Particular Reference to Experimental Hemorrhage and Burn Shock, Ann. Surg. **118**:193-214 (Aug.) 1943. (*b*) Koop, C. E.; Riegel, C.; Vars, H. M.; Ratcliffe, H. L.; Parkins, W. M., and Lockwood, J. S.: Studies on Gelatin as a Plasma Substitute: II. Observations on Toxicity and Elimination of Gelatin, Am. J. M. Sc. **205**:876-877 (June) 1943.

6. Lowell, A.; Colcher, H.; Kendall, F. E.; Patek, A. J., Jr., and Seegal, D.: A Comparison of the Effects of High and Low Viscosity Gelatins After Their Intravenous Injection in Man, J. Clin. Investigation **25**:226-236 (March) 1946.

eosinophilic precipitation in Bowman's space when the tissues were fixed with Zenker's solution.

Jacobson and Smyth [7] found no change in urea clearance in 5 patients after infusion of a bone gelatin. Popper's group [8] found no histologic changes in kidneys in seven autopsies after infusion of gelatin in man. Morehead and Little [9] found an inflammatory lesion present in the kidney in more than one half of 9 dogs which received infusions of a bone gelatin. This lesion represented to them the interstitial nephritis commonly seen in dogs and described by Bloom.[10]

Oliver,[11] using a microdissection technic, revealed no instance of frank evidence of tubular epithelial damage such as necrosis of the cells. Administration of gelatin caused only a transient loculation in the proximal convoluted tubules in the kidney. Chemical identification of these droplets was not possible; however, one can assume that they were due to reabsorbed gelatin which attracted water and caused the hydropic swelling which morphologically simulates that produced by sucrose.[11a]

The renal histologic sections described by Skinsnes [4] can only mean that some substance is being vigorously reabsorbed or excreted by the proximal tubule cells. Oliver [11] has shown that the concept of "hydropic degeneration" simply means that eosinophilic granular material (e. g., albumin) appearing in the glomerular filtrate is being reabsorbed by the proximal tubular cells. Since it is now known that a certain amount of albumin with diameters of 150 by 38 angstrom units normally passes through the glomerular membrane,[12] gelatin with a

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7. Jacobson, S. D., and Smyth, C. J.: Gelatin as a Substitute for Plasma: Observations on Its Administration to Human Beings, Arch. Int. Med. **74**:254-257 (Oct.) 1944.

8. Popper, H.; Volk, B. W.; Meyer, K.; Kozoll, D. D., and Steigmann, F.: Evaluation of Gelatin and Pectin Solutions as Substitutes for Plasma in the Treatment of Shock, Arch. Surg. **50**:34-45 (Jan.) 1945.

9. Morehead, R. P., and Little, J. M.: A Morphological Study Following the Intravenous Administration of Gelatin Solutions to Dogs, Am. J. Path. **21**:333-338 (March) 1945.

10. Bloom, F.: Classification and Pathology of Renal Disease in Dog: Comparison with Nephritis in Man, Arch. Path. **28**:236-245 (Aug.) 1939.

11. Oliver, J., in a report to the National Research Council, Division of Medical Sciences, Committee on Blood Substitutes, September 1943.

11a. Anderson, W. A. D., and Bethea, W. R., Jr.: Renal Lesions Following Administration of Hypertonic Solutions of Sucrose: Report of Six Cases, J. A. M. A. **114**:1983-1987 (May 18) 1940.

12. Oliver, J.: New Directions in Renal Morphology: A Method, Its Results and Its Future, in Harvey Lectures, 1944-1945, Baltimore, Williams & Wilkins Company, 1946, pp. 102-155. Smetana, H.: The Permeability of the Renal Glomeruli of Several Mammalian Species to Labelled Proteins, Am. J. Path.

*(Footnote continued on next page)*

smaller diameter of 18 angstrom units will be found in the glomerular filtrate. Thus Skinsnes' sections may represent the proximal tubule reabsorption of gelatin, especially since it can be demonstrated in the plasma seven to twelve days after its administration.

The absence of cellular degeneration as indicated by lack of necrosis in the proximal tubules or of degeneration of the brush border would indicate that marked tubular damage did not occur, especially since gelatin was probably present in the plasma of the patients at death.

The routine clinical studies of renal function and urea clearance, phenolsulfonphthalein and concentration tests are qualitative. In a recent study of the nephrotoxicity of an antibiotic, 20 to 80 per cent reduction in renal plasma flow, glomerular filtration rate, maximal tubular excretion of p-aminohippurate and maximal tubular reabsorption of phosphate occurred, while there were no statistically significant alterations in blood urea nitrogen or phenolsulfonphthalein and urea clearance.[13]

Since the qualitative tests of renal function are not sensitive enough to pick up even major aberrations in renal function and since casts appear in the urine only intermittently and are easily overlooked quantitative renal function tests should be performed completely to rule out nephrotoxicity.

A program to test the quantitative renal function following infusion of gelatin is now under way in this laboratory.

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HERBERT L. RATCLIFFE, Sc.D.
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**23**:255-267 (March) 1946. Terry, R.; Hawkins, D. R.; Church, E. H., and Whipple, G. H.: Proteinuria Related to Hyperproteinemia in Dogs Following Plasma Given Parenterally: A Renal Threshold for Plasma Proteins, J. Exper. Med. **87**:561-573 (June) 1948.

13. Michie, A. J.: Am. J. M. Sc., to be published.

# SURGICAL IMPLICATIONS OF ACUTE PANCREATITIS

## An Analysis of Eighty-Five Cases

J. G. PROBSTEIN, M.D.
S. H. GRAY, M.D.
L. A. SACHAR, M.D.
AND
W. J. RINDSKOPF, M.D.
ST. LOUIS

THE RECOGNITION of increased blood diastase values in instances of acute pancreatitis by Elman [1] and the subsequent development of a simple, rapid and accurate method of determining the diastatic activity of both blood and urine by Somogyi [2] have led to the more frequent recognition of mild or transient forms of this disease.

A decade ago this subject was reviewed, and case reports of 21 patients with acute pancreatitis seen at St. Louis Jewish Hospital and St. Louis City Hospital were presented in a paper from these laboratories.[3] From 1934, when the Somogyi diastase methods were first used, until July 1947 there have been 65 patients with acute pancreatitis seen at the St. Louis Jewish Hospital. The history of these patients subsequent to their attacks of pancreatitis is available in most instances. As the cases accumulated, characteristics of the disease which we did not previously appreciate have become more apparent and the place of surgical procedures has become more clearly defined.

### INCIDENCE

The incidence of acute pancreatitis is much greater than is usually recognized. Thus, during the period in which 65 patients with acute pancreatitis were seen, 51,500 patients were admitted to the surgical

Aided by the David May-Florence G. May Research Fund.

From the Department of Surgery and the Laboratory of the Jewish Hospital and the Department of Surgery, Washington University School of Medicine.

1. Elman, R.; Arneson, N., and Graham, E.: Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec.) 1929.

2. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399, 1938.

3. Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Transient Acute Pancreatitis, Ann. Surg. **108**:1029, 1938.

and medical services of the hospital. Some of them were admitted with acute pancreatitis on several occasions, and 1 patient had two attacks during the same period in the hospital. Of these 51,500 patients, 84 were admitted for acute pancreatitis. Hence, about 1 out of 600 patients admitted to the surgical and medical services had acute pancreatitis. The true incidence in this hospital is probably even greater, because in the first years of this series many cases were undoubtedly overlooked.

This figure is to be contrasted with that reported by Fallis and Plain [4] in 1939. They reported an incidence of 1 case of pancreatitis in every 10,000 persons admitted when the diagnosis of pancreatitis was based on the findings at operation and preoperative diagnostic determinations of the blood diastase were not performed. It is readily apparent what valuable diagnostic adjuncts determinations of blood and urine diastase are and how easy it is to overlook mild transient forms of acute pancreatitis. In this hospital it has become routine to order a determination of the blood diastase in any case in which pain in the upper abdominal area is presented.

### ASSOCIATION WITH DISEASE OF THE GALLBLADDER

The association of acute pancreatitis with disease of the gallbladder is so well known as to be hardly worth repeating. Some aspects of this relationship have not been sufficiently stressed.

There is a significant number of patients with acute pancreatitis who have a coincident acute cholecystitis. McWhorter [5] reported that 22 per cent of patients with acute pancreatitis had acute cholecystitis. Fallis and Plain,[4] on the basis of operative findings, found the incidence to be 15.4 per cent. Lewison [6] reported an incidence of 3 per cent. McCorkle [7] reported that 22 per cent of patients with acute pancreatitis had a coincident acute cholecystitis.

A review of the physical findings leads us to suspect concurrent acute cholecystitis on clinical grounds in 16 of 85 episodes of pancreatitis. Actually, 15 episodes of pancreatitis occurred after cholecystectomy. Hence 16 of a possible 70 patients presumably had concurrent acute cholecystitis, an incidence of 23 per cent. However, we are unable to state with certainty how many of our patients with acute pancreatitis had concurrent acute cholecystitis, because early operation is not the accepted practice in this hospital in cases of acute cholecystitis or acute pancreatitis.

4. Fallis, L. S., and Plain, G.: Acute Pancreatitis, Surgery **5**:358, 1939.

5. McWhorter, G. L.: Acute Pancreatitis, Arch. Surg. **25**:958 (Nov.) 1932.

6. Lewison, E. F.: Acute Pancreatitis, Arch. Surg. **41**:1008 (Oct.) 1940.

7. McCorkle, J., and Goldman, L.: The Clinical Significance of the Serum Amylase Test in the Diagnosis of Acute Pancreatitis, Surg., Gynec. & Obst. **74**:439, 1942.

During the period in which these patients were seen, 121 patients with acute cholecystitis, inclusive of the 16 mentioned previously, were seen. Thus, 13 per cent of the patients with acute cholecystitis had concurrent pancreatitis. McCorkle and Goldman [7] found that 14 of 42 patients with cholecystitis had concurrent pancreatitis.

This significant correlation between acute pancreatitis and acute cholecystitis has three possible explanations:

1. The acute cholecystitis causes the acute pancreatitis.
2. The acute pancreatitis causes the acute cholecystitis.
3. Both the acute pancreatitis and the acute cholecystitis are caused by a third factor common to both.

The first explanation can hardly hold in all cases, because acute pancreatitis occurs not uncommonly in persons whose gallbladder has been previously removed. As stated before, fifteen of the attacks of pancreatitis in our series occurred in 11 persons whose gallbladders had been removed.

It is not readily apparent how acute pancreatitis could cause acute cholecystitis.

The third explanation, that the relationship between acute cholecystitis and acute pancreatitis is due to a common etiologic factor, seems more tenable. The common factor would seem to be obstruction distal to the junction of the pancreatic and common bile ducts converting them into a "common channel." Thus Bisgard and Baker [8] were able to produce concurrent acute pancreatitis and acute cholecystitis experimentally by obstructing the common duct of goats distal to the entrance of the pancreatic duct.

That there actually is a reflux of pancreatic juice into the gallbladder during an acute attack of pancreatitis was shown in 1933 by Popper,[9] who found increased amounts of diastase in the gallbladder bile in 15 of 16 patients with acute pancreatitis. Since the gallbladder bile does not normally contain diastase,[10] the diastase must have gotten into the gallbladder by reflux through a common channel. These observations, which can only be explained by the "common channel" theory of pancreatitis, have been confirmed by us in 2 patients with acute pancreatitis operated on at this hospital since the series was collected. One case is presented here in detail:

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8. Bisgard, J. D., and Baker, C. P.: Studies Relating to Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, Ann. Surg. **112**:1006, 1940.

9. Popper, H. L.: Pankreassaft in den Gallenwegen: Seine pathogenetische Bedeutung für die Entstehung der akuten Pankreaserkrankungen, Arch. f. klin. Chir. **175**:660, 1933.

10. Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Clinical Studies on Blood Diastase, Arch. Int. Med. **67**:805 (April) 1941.

D. B., a 59 year old woman, entered the hospital on July 11, 1947, with a history of attacks of sharp epigastric pain occurring during the preceding three years. These pains had become more frequent during the preceding three weeks; they started in the mid-epigastrium and radiated to the flanks. The pain had always been associated with nausea. During the past year the patient had lost 12 pounds (5.4 Kg.).

On her admission to the hospital the blood diastase was 59 units; the white blood cell count was 5,000. The temperature, pulse and respirations were normal. There was epigastric tenderness. Two days after her admission the patient suddenly had severe epigastric pain, more severe than any she had experienced in the past. Glyceryl trinitrate failed to relieve it. Administration of pantopon® (a mixture of the hydrochlorides of the opium alkaloids) ⅓ grain (0.02 Gm.) gave considerable relief. The blood diastase level on that day was 1,580 units. The pain persisted during the next day. There was diffuse muscle guard and tenderness over the entire abdomen, but it was most marked in the upper region and particularly in the right upper quadrant. There was a questionable mass in the right upper quadrant, but the muscle guard prevented adequate palpation.

On the second day of this acute episode the diastase level was 1,900 units. The white blood cell count had risen to 26,000. Bile and urobilinogen (3 plus) were present in the urine. The icterus index was 30. The reaction to the van den Bergh indirect test was positive. On the night of the second day the abdomen was explored. It contained yellowish-tinged free fluid. The liver was enlarged and the edge rounded. The gallbladder was fiery red and extremely thin. The pancreas was enlarged, and the serosa over it was edematous.

The gallbladder was aspirated and the contents sent to the laboratory for culture and for determination of the diastase and nitrogen content. A biopsy of material from the pancreas was made. A cholecystostomy was then performed. The blood diastase level was obtained at the time of operation.

The postoperative convalescence was uneventful. The pancreatic biopsy showed the characteristic findings of "acute interstitial pancreatitis." The gallbladder bile, which normally contains no diastase, contained 1,095 units. Its nitrogen content was 1.17 per cent. The blood diastase level, obtained simultaneously, was 430 units. Culture of the contents of the gallbladder revealed Bacillus coli.

The obvious explanation of the finding of diastase in the gallbladder is that there was a reflux of pancreatic juice into the gallbladder. An alternate explanation might be advanced. It might be argued that the presence of diastase was due to transudation from the gallbladder wall as part of the process of inflammation. That this explanation does not hold is shown by the finding of a higher concentration of diastase in the gallbladder bile than in the blood. Furthermore, it cannot be said that the inflammatory exudate was concentrated in the gallbladder by absorption of water, thus accounting for the higher diastase level, because the protein content of the material in the gallbladder was less than that of the blood plasma.

Popper also found that the diastase content of gallbladder bile was higher than that of the blood during acute pancreatitis.[9]

### CLINICAL FEATURES OF ACUTE ATTACKS

An analysis of the physical findings in our series fails to reveal any constant distinctive pattern which would enable the diagnosis to be made with certainty without exploration or determination of serum or urine

diastase levels. The pain is usually epigastric. It may radiate to the right or to the left, to the back or to the shoulders. Often it was "cramping" or "colicky" in character. The severity varied, but morphine was usually required for relief. About half of the patients vomited, and most of the remainder were nauseated. Prostration is the rule, and the patients take to bed voluntarily. Epigastric tenderness is an almost constant finding. In addition, there may be tenderness in the left or right upper quadrant. In some cases there is generalized abdominal tenderness. Muscle guard is variable. Cases presenting tenderness in the right upper quadrant and muscle guard are indistinguishable from cases of acute cholecystitis. Indeed, there may actually be a concomitant acute cholecystitis. At times an ill defined, tender mass may be felt in the right upper quadrant. In 1 case this proved to be liver rather than gallbladder at operation, although the gallbladder was inflamed. The temperature is elevated only moderately. In some cases the elevation is slight.

The white blood cell count is increased but not markedly, and counts of over 18,000 are not common. Counts of 8,000 to 11,000 are not unusual. The icterus index is usually increased.

The distinctive laboratory finding is an increased blood and urinary diastase level. The significance of determinations of blood and urine diastase has been previously reviewed by Elman,[11] Gray, Probstein and Heifetz [3] and Lewison [6] among others.

### PROGNOSIS

The immediate prognosis after an attack of pancreatitis in our series was good. There were 3 deaths in the eighty-five attacks of pancreatitis. Two deaths occurred on the second day of the disease, while the third death occurred on the twenty-fourth day.

There is, however, a great tendency for the disease to recur. Its recurrent nature has been mentioned by a number of authors. Love [12] in 1926 emphasized that in 31 of the 51 cases he reported there was a history of previous attacks. Elman [11] also emphasized the recurrent nature of the disease. He reported 38 cases of transient pancreatitis, 4 of his own and 34 from the literature; in 24 there had been previous attacks. Fallis and Plain [4] noted that 53.8 per cent of their 26 patients had similar pain in the past. Lewison [6] reported 71 per cent of his 35 patients had a history of previous attacks.

These previous attacks for the most part have been considered to be pancreatitis because of their similarity to an attack which was posi-

11. Elman, R.: Acute Interstitial Pancreatitis, Surg., Gynec. & Obst. **57:** 291, 1933.

12. Love, R. J.: Acute Pancreatitis, Lancet **2:**1262, 1926.

tively diagnosed either by exploration or by the finding of high blood diastase values. The validity of a diagnosis of previous attacks on such a basis is always open to question in the absence of operative findings or of a high blood diastase level. Occasionally when patients are questioned closely, they will state that the "similar attacks" in the past were not really as severe as the one during which the diastase level was increased. There is a possibility, therefore, that some of these "previous attacks" based on history were really not pancreatitis.

Nevertheless, of our 65 patients with pancreatitis, 14 have been observed during recurrent attacks of pancreatitis, verified by the finding of a high blood diastase level. Another 15 patients gave a history of one or more similar attacks in the past.

Because of the questionable character of a diagnosis of pancreatitis based on history alone, we have confined our further analysis of these recurrent cases to those in which increased blood or urine diastase levels were actually found on several occasions.

The interval between these attacks is given in the table. Before,

*Interval Between Attacks*

| Patient | First and Second Attack, Mo. | Second and Third Attack, Mo. |
|---|---|---|
| R. G. | 3½ | 6½ |
| M. E. | 1 | |
| C. E. | 42 | |
| M. F. | 11½ | |
| C. C. | 6 | |
| E. K. | ¼ | |
| T. C. | 5½ | |
| S. C. | 30 | |
| I. K. | 32 | 4 |
| B. S. | ¼ | |
| R. S. | 4 | 2 |
| I. L. | 42 | |
| G. F. | 2 | |

after or between "verified" attacks of pancreatitis the patient may have epigastric pains during which the blood diastase is normal. The pathogenesis of these pains is not known. It is possible that these attacks may be pancreatitis but that the rise in the diastase level was too evanescent to be discovered.

The sequelae of these episodes of acute transient pancreatitis have been of particular interest to us since the recent description of "chronic relapsing pancreatitis" by Comfort and his co-workers.[13] These authors described cases of steatorrhea, diabetes and pancreatic calculi following

13. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis, Gastroenterology **6**:239, 1946.

recurrent abdominal pain. The episodes of abdominal pain described frequently did not correspond to what we have considered to be the typical clinical picture of acute transient pancreatitis. Reports of the blood diastase level during the acute attacks were lacking in most cases, and in some it was normal. As we have previously stated, a diagnosis of acute pancreatitis of the "edematous" or "hemorrhagic" type is questionable without the finding of an increased blood diastase level at least during the beginning of the attack. Comfort, Gambell and Baggenstoss have suggested that the interstitial fibrosis and atrophy of the parenchyma, which pathologically characterizes "chronic relapsing pancreatitis," may be due to repeated attacks of acute interstitial inflammation of the pancreas. It is therefore of considerable interest to find that the clinical evidences of chronic pancreatitis described by these authors have not been found in the follow-up of our series of cases of acute pancreatitis. We are now reviewing our cases of chronic pancreatitis diagnosed histologically at operation or at autopsy.

## TREATMENT

Since 1934 it has been the generally accepted policy of surgeons at this hospital not to operate during the acute episode of pancreatitis, no distinction being made between hemorrhagic and interstitial pancreatitis. On two occasions this policy was disregarded and the patients were operated on after a diagnosis of pancreatitis was made. In 1 case acute hemorrhagic pancreatitis was found. The patient died on the day of operation. The other patient recovered uneventfully.

The other 83 patients with attacks of pancreatitis were treated conservatively. There were 2 deaths in this group. One patient, aged 75, died on the second day of her disease. Autopsy was not permitted. The other fatality occurred twenty-four days after the onset of the acute pancreatitis. At autopsy an abscess in the head of the pancreas and multiple abscesses of the liver were found.

Although surgical intervention is not indicated in the treatment of the acute attack, exploration does seem to be warranted when inflammatory signs and symptoms persist. Then the operative procedure is really directed at the complications of acute pancreatitis rather than at the pancreatitis itself. It might have been possible to avoid one of the fatalities in this series had this rule been followed. Since this series was collected we have observed 1 case which illustrates the place of "delayed surgery" in the treatment of acute pancreatitis.

C. B., a 79 year old woman, was admitted to the Jewish Hospital on Sept. 11, 1947. Four weeks earlier, while in Frankfort, Mich., she had an attack of severe abdominal pain, colicky in nature, accompanied with fever. She was given sulfonamide compounds and then penicillin. However, she continued to have

constant nausea, indigestion and epigastric discomfort. She had a temperature of up to 102 F. daily.

Examination at the time of her admission to this hospital revealed a fairly alert elderly woman. She had a systolic murmur at the apex. The liver was felt extending 4 fingerbreadths below the costal margin. There was a sense of resistance in the epigastrium imparted to the palpating hand, but no mass was felt.

A series of roentgenograms showed a nonfunctioning gallbladder. No calculi were seen. A gastrointestinal series was interpreted as showing "an extrinsic mass lying in the midline and exerting pressure on the distal end of the stomach without displacing the duodenum." The white blood cell count was 12,400, with a left shift in the differential count. The blood nonprotein nitrogen was 33 and the serum diastase less than 20 units.

On September 17 the upper region of the abdomen was explored through a transverse abdominal incision. The transverse colon and the stomach were fixed to a mass in the head of the pancreas. The gallbladder contained stones. The pancreatic mass was broken into through the transverse mesocolon. A small amount of purulent material was obtained, and then a large piece of necrotic material was removed with a sponge forceps. The cavity left by the removal of this material was drained with a cigaret drain brought out through the wound. The abdomen was closed in layers about the drain. Culture of the abscess revealed B. coli. Postoperatively the patient was given penicillin and streptomycin. She was out of bed on the second postoperative day. Her convalescence has been uneventful.

After the attack of acute pancreatitis has subsided the question of cholecystectomy frequently arises, particularly if the Graham test reveals gallstones or a nonfunctioning gallbladder. Fifty-six persons in this series had not undergone an operation on the biliary tract before being observed in an attack of acute pancreatitis. Twelve of these patients subsequently were subjected to operation. All of them underwent cholecystectomy and 6, in addition, explorations of the common duct. In 2 cases stones were found in the common duct. Two of the 12 patients in whom operations on the biliary tract had been performed subsequently were hospitalized for recurrence of pancreatitis. The first patient had recurrences of pancreatitis seven and twelve months after her gallbladder had been removed and her common duct explored. No stones had been found in the common duct. The second patient had her gallbladder removed and three stones removed from the common duct. After a few months she began to have frequent epigastric pains, but not until five years later did she have an attack of pancreatitis verified by a high blood diastase level. Two months later she had another attack of acute pancreatitis with an increase in the blood diastase. Her common duct was reexplored and found to be free of stones. She continued to have the vague epigastric pains which followed her original surgical procedure. These pains occurred even though the T tube, which was placed in her common duct, was left open.

In addition to the 2 patients described who had recurrent acute pancreatitis after cholecystectomy, there were 9 other patients who had acute pancreatitis after undergoing cholecystectomy. Whether these attacks represent recurrences or first attacks is not known.

It is clear that cholecystectomy, with or without exploration of the common duct, in our experience has not been a certain means of preventing acute pancreatitis. Hence, in regard to the decision whether cholecystectomy is indicated after an attack of acute pancreatitis, it appears that if one would have advised cholecystectomy had pancreatitis not developed then one should, of course, continue to advise cholecystectomy. On the other hand, if the history and the roentgenologic findings are such that one would not have advised cholecystectomy had acute pancreatitis not ensued, then one should continue to advise against removal of the gallbladder.

When cholecystectomy is performed after an attack of acute pancreatitis, we believe that the common duct should be explored. In two of the six common ducts that were explored after attacks of acute pancreatitis stones were found. Moreover, should the pancreatitis recur after the surgical procedure, as seems to happen not uncommonly, the question arises of whether a stone in the common duct has been overlooked. It is some comfort to the surgeon to know that he had previously explored the common duct.

It is in the handling of cases in which pancreatitis has developed after cholecystectomy that the most difficult problems arise. The question then is whether to explore or reexplore the common duct.

Of our 11 patients who had acute pancreatitis after a cholecystectomy, in only 1 was reexploration carried out. Nothing was found in or about the common duct to account for the pancreatitis. Of the 10 who were treated expectantly, 5 had proved multiple attacks, but eventually all became free of abdominal pain without surgical intervention.

During July 1947 there had been another patient, not included in this series, who had acute pancreatitis nine years after a cholecystectomy. Her common duct was explored after subsidence of the pancreatitis. Nothing was found.

Our experience would indicate that the occurrence of acute pancreatitis subsequent to a cholecystectomy is not an indication in itself for exploration or reexploration of the common duct.

## SUMMARY

Acute pancreatitis is not an uncommon disease, but it will be frequently overlooked if determinations of blood or urine diastase are not made in all cases of pain in the upper abdominal area. Frequently there is a coincident acute cholecystitis. The existence of a "common channel"

formed by the pancreatic and common bile ducts seems to be an etiologic factor common to the acute pancreatitis and coincident acute cholecystitis. The finding of a reflux of pancreatic juice into the gallbladder during an attack of acute pancreatitis has been confirmed. Acute pancreatitis, as a rule, subsides spontaneously but tends to recur in about half of the cases. Cholecystectomy, with or without exploration of the common duct, does not prevent the recurrence or onset of acute pancreatitis. The development of acute pancreatitis after a cholecystectomy is not an indication for exploration or reexploration of the common duct. In our experience recurrent pancreatitis has tended to be a self-limited disease. We have had no case in which it progressed to chronic pancreatitis.

# EFFECT OF GASTRECTOMY AND DIVERSION OF DUODENAL SECRETIONS INTO THE TERMINAL PORTION OF THE ILEUM ON DEVELOPMENT OF ULCER

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THE FAILURE of bilateral supradiaphragmatic vagotomy to protect against the development of ulcer in the Mann-Williamson dog, as recently reported,[1] has been the stimulus for the work herein described. This investigation was conducted to determine (1) the effect of total gastrectomy with diversion of the duodenal secretions into the terminal portion of the ileum on the development of ulcer and (2) to determine the possible existence of another factor besides the role of acid in the formation of ulcer in man.

The role of acid in the production of ulcer appears to be too definite [2] to be disputed, and it is also well known that vagotomy produces in the dog a definite decrease in the amount of acid and in the total volume of gastric secretion.[3] However, the failure of vagotomy to protect against the development of ulcer in the Mann-Williamson dog led my colleagues and me to believe that the acid might not be the sole cause of ulcer. The possibility of the presence of another factor of great importance, which might be contained in bile or in pancreatic or duodenal secretion or in all three, exists, since in the Mann-Williamson operation [4] all three secretions are diverted from their usual location just distal to the stomach where experimental ulcers are located, into the terminal portion of the ileum 15 cm. from the ileocecal junction. The beneficial effects on patients with ulcers to whom are administered extracts of the duodenum and upper part of the jejunum, as reported by Ivy [5] and his

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1. Oliver, J. V.: Effect of Vagotomy on Development of the Mann-Williamson Ulcer in the Dog, Arch. Surg. **55**:180, (Aug.) 1947.

2. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcers, Surg., Gynec. & Obst. **55**:265, 1932.

3. Hartzell, J. B.: The Effect of Section of the Vagus Nerves on Gastric Acidity, Am. J. Physiol. **91**:161, 1929.

4. Mann, F. S., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

5. Ivy, A. C.: The Prevention of Recurrence of Peptic Ulcer: An Experimental Study, Gastroenterology **3**:443, 1944.

associates, offer proof that the correction of other possible factors exclusive of the hyperacid one may relieve ulcer in man.

The Mann-Williamson operation for internal duodenal drainage shunts the three secretions into the terminal portion of the ileum approximately 15 to 25 cm. from the ileocecal junction, depriving the experimental animal of their action at the site intended for their full physiologic effect. The loss of these three important secretions explains the ulcers which develop in practically 100 per cent of all experimental animals on which the Mann-Williamson operation is performed.

The question arises of whether the stomal ulcer is due to the action of the gastric juices on the susceptible jejunal mucosa or to the lack of alkaline buffering biliary and pancreatic and duodenal secretions or the physiologic loss of some other important factor found in one or all of the three secretions.

Connell [6] performed a fundusectomy, removing an inverted V-shaped wedge comprising the middle two quarters from the greater curvature of the dog's stomach. The animals were kept under observation for a period of three months, after which they were killed and the following observations made:

1. Gastric motor emptying time was not changed after eight weeks.

2. The size and shape of the stomachs returned to normal after six weeks, with gastric capacity restored to preoperative volume.

3. Within three months gastric acid levels were back to normal and equal to preoperative levels.

4. Histologically, no increase in the number of parietal cells was noted to explain the return of the secretory levels to normal.

Ivy and Fauley [7] performed a fundusectomy, as described, in a series of 13 dogs on whom they had performed a Mann-Williamson operation and fed them a diet of ground raw liver, ground raw pancreas, prepared dog food (pard®) and milk. Seven lived one year, and the remaining 6 lived two years in good nutritional state. At necropsy it was noted that in none of the 13 experimental animals did stomal or jejunal ulcers develop. A return to normal of the gastric acid values was also noted. In a second group of 11 fundusectomized Mann-Williamson dogs fed a stock diet, the average survival time was ten weeks and stomal ulcers were found in 3 of the 11. At necropsy it was observed that the gastric remnant had hypertrophied to approximately the preoperative normal size and the gastric acid values had returned to normal.

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6. Connell, F. G.: Fundusectomy: Experimental, Surg., Gynec. & Obst. **53**:750, 1931.

7. Fauley, G. B., and Ivy, A. C.: The Prevention of Postoperative Jejunal Ulcers, Surg., Gynec. & Obst. **63**:717, 1936.

They concluded that fundusectomy has a prophylactic value in preventing ulcer in the Mann-Williamson dog fed a stock diet and that the special diet prevented the development of the Mann-Williamson ulcer in a fundusectomized animal.

The value of a special diet in delaying the onset of the Mann-Williamson ulcer is to a great extent due to the maintenance of a high degree of nutritional state, but eventually ulcers are inevitable, and if the experimental animal survives long enough a stomal ulcer will develop.

Mann [8] stated that after fundusectomy there is a decrease in the degree of gastric acidity roughly parallel to the amount of stomach removed. There is, however, a return to normal in a few months. No one has been able to determine if the quantity of acid is permanently changed by fundusectomy. In their series of 12 dogs which survived a subtotal gastrectomy with removal of 66 per cent of the stomach for three months or more, jejunal ulcer developed in 7. Hypertrophy and dilatation of the gastric remnant occurred in 6 of the 12 animals. Gastric acidity after three to six months approximated the values for the controls. Gastric motor emptying time, however, was reduced from four and a half to two and a quarter hours.

The effects produced by drainage of the duodenal, biliary and pancreatic secretions back into the stomach following an end to end gastrojejunostomy with closure of the proximal duodenal limb and suturing of the terminal duodenum end to side into the stomach were studied by McCann,[9] who noted the development of jejunal ulcer in 80 per cent of 26 dogs in from one to three months. The ulcers were single, 6 to 10 mm. in diameter, and situated beyond the suture line, and they resembled the human peptic ulcer. In spite of the alkaline buffering effect of the duodenal secretions and the presence of a possible antiulcer factor in these secretions, a stomal ulcer developed which could be explained only on the basis of an increased susceptibility of the jejunal mucosa or the prolonged secretion of a highly acid gastric juice due to liberation of histamine following operation.

Fauley and Ivy,[10] in a series of Mann-Williamson dogs, delayed the onset of the development of ulcer by administration of an alkaline phosphate gel.

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8. Mann, F. C., cited by Connell.[6]

9. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

10. Fauley, G. B., and Ivy, A. C.: An Attempt to Prevent Postoperative Jejunal Ulcers by Aluminum Hydroxide Therapy: An Experimental Study in Mann-Williamson Dogs, Am. J. Digest. Dis. **5**:792, 1936.

In discussing the problem of fundusectomy in the treatment of peptic ulcer, Seeley and Tollinger,[11] after a series of observations on fundusectomized animals, concluded that fundusectomy had nothing to offer as a means of permanently reducing gastric acidity.

## METHODS OF EXPERIMENTAL PROCEDURE

This investigation was divided into two experimental procedures. All animals were permitted to survive for their life span after (1) partial or "subtotal" gastrectomy with removal of three fourths of the stomach and diversion of the duodenal secretions, bile and pancreatic juice into the terminal portion of the

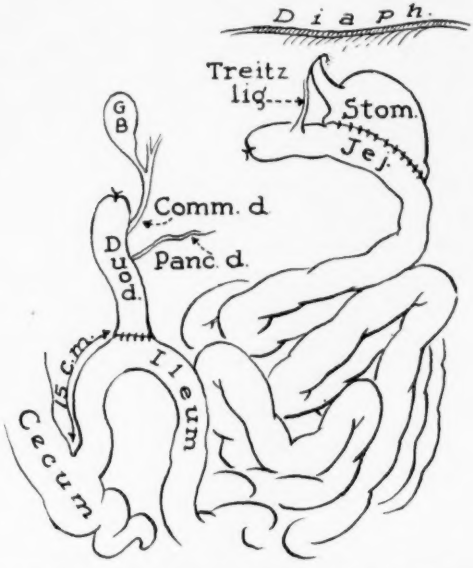


Fig. 1.—A partial or "subtotal" gastrectomy (leaving 25 per cent of the stomach), with anastomosis of the stomach to the jejunum was performed just distal to the ligament of Treitz. A Mann-Williamson operation was then performed, the distal portion of the duodenum being transplanted into the distal end of the ileum. (For results regarding ulcer formation, see table 1, series A.)

ileum and (2) "total" gastrectomy followed by shunting of the duodenal contents into the terminal end of the ileum. On arrival, all animals were quarantined for a period of ten days and placed on a stock diet of purina dog chow® and water. Preoperatively, no therapeutic or dietary measures were utilized to condition the animal. Postoperatively, diet consisted of milk for three days, after which they were fed a ration of pard,® 400 Gm.; ground raw pancreas, 200 Gm.; ground raw

11. Seeley, H., and Tollinger, R.: Fundusectomy in the Treatment of Peptic Ulcer, Surg., Gynec. & Obst. **61**:155, 1935.

liver, 200 Gm., and milk, 200 cc. We used this improved diet because the experimental animals experienced great difficulty in maintaining their nutritional state on a diet of purina dog chow® alone and perished within too short a period (usually two weeks) for the results to be of statistical significance. It is evident that an experimental animal deprived of a stomach, and with its duodenal contents drained into the terminal portion of the ileum, is in dire need of all possible nutritional factors to prevent early death. However, no other postoperative medication or therapeutic measures were used. Animals surviving less than thirty days were not used in evaluating the results of our experiments, since it is clearly manifest that these animals had succumbed too soon after the operation to be used in the experiments; many of them died at operation.

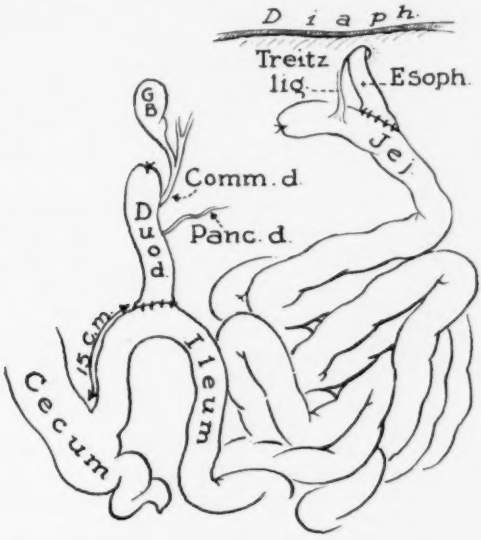


Fig. 2.—A "total gastrectomy" (except for a cuff 1 to 2 cm. wide) was performed, the esophagus or cuff of cardia being anastomosed to the jejunum just distal to the ligament of Treitz. At a second stage three weeks later, a Mann-Williamson operation anastomosing the terminal end of the duodenum to the ileum was performed. (For results regarding ulcer formation, see table 2, series B.)

*Series A. "Subtotal" Gastrectomy with Diversion of the Duodenal Secretions into the Terminal Portion of the Ileum.*—The first series comprises 10 animals subjected to a partial or "subtotal" gastrectomy and diversion of the duodenal secretions performed as follows: Under anesthesia produced by morphine and the intraperitoneal administration of pentobarbital sodium, the duodenum was transected at its pyloric juncture and the distal stump inverted. The jejunum was transected just distal to the duodenojejunal flexure at the ligament of Treitz. The distal limb of the jejunum was inverted and closed and the proximal limb sutured end to side into the terminal portion of the ileum, approximately 15 cm. from the

ileocecal juncture. Excision of the pylorus and 75 per cent of the fundus was then performed, with an end to side gastrojejunostomy (fig. 1). In this series, 4 animals survived the operation thirty days or more; the experimental data herein analyzed are derived only from this surviving group, which admittedly is small.

*Series B. "Total" Gastrectomy with Diversion of the Duodenal Secretions into the Terminal Portion of the Ileum.*—In this second experimental group, or series B, the operation was performed in two stages. In the first stage a "total" gastrectomy was performed as follows: Under morphine and intraperitoneal anesthesia, the duodenum was transected at its pyloric juncture and the distal stump inverted. The ligament of Treitz was incised, the duodenojejunal flexure being mobilized. The stomach was then totally extirpated (except for a small cuff of cardia), after which the cardia was anastomosed end to side into the jejunum, slightly distal to a point where the ligament of Treitz had crossed it. Because of the anatomic configuration of the diaphragm in the dog and the lack of mobility of the lower part of the esophagus, it is almost impossible for the animal to recover after absolute and total gastrectomy. However, only a small cuff of cardia just sufficient to allow for suturing to the jejunum remained. The width of the cuff

TABLE 1.—*Subtotal Gastrectomy with Duodenal Secretions Shunted into the Distal End of the Ileum*

| Dog | Weight, Lb. | Date of Operation | Date of Death | Survival Time, Days | Weight Loss, Lb. | Comment |
|---|---|---|---|---|---|---|
| 1 | 11 | 12/22/1946 | 1/24/1947 | 33 | 4 | Jejunal ulcer 3 cm. by 8 mm.; ulcer not perforated; death due to inanition |
| 2 | 20 | 12/27/1946 | 2/12/1947 | 47 | 8 | Jejunal ulcer 1 cm. by 8 mm. not perforated |
| 3 | 18 | 1/10/1947 | 3/13/1947 | 62 | 5 | Jejunal ulcer 1.5 by 1.2 cm. perforated; peritonitis |
| 4 | 21 | 1/24/1947 | 4/ 3/1947 | 68 | 6 | Jejunal ulcer 1.4 by 1.2 cm. perforated; peritonitis |

remaining approximated the width of the stomach clamp, usually 1 cm. This amount of cardia would represent less than 2 per cent of the total stomach. Our experience concurs with that of Mann [12] in this respect.

After a recovery period of approximately two to three weeks, the second stage, consisting of shunting of the duodenal secretions into the distal end of the ileum as previously described, was performed.

Eight animals survived both the preliminary complete gastrectomy and the subsequent operation for diversion of duodenal secretions into the terminal portion of the ileum. Only the data on experimental animals surviving the second operation thirty days or more are analyzed.

## RESULTS

*Series A.*—Among the 4 animals analyzed in this series, death occurred thirty-three, forty-seven, sixty-two and sixty-eight days respectively after operation, the average period of survival being fifty-two days (table 1). At necropsy all animals presented a stomal ulcer. In 2

12. Mann, F. C.: Gastrectomy: An Experimental Study, Ann. Surg. **95**:455, 1932.

cases the ulcer had perforated, causing death by peritonitis. The ulcers were round or oval and sharply punched out with terraced edges, each step in the terrace representing successive invasion of the deeper layers of the jejunal wall, and the bases were hard and indurated. The ulcers were approximately 1 cm. in diameter, except for one which was oval in

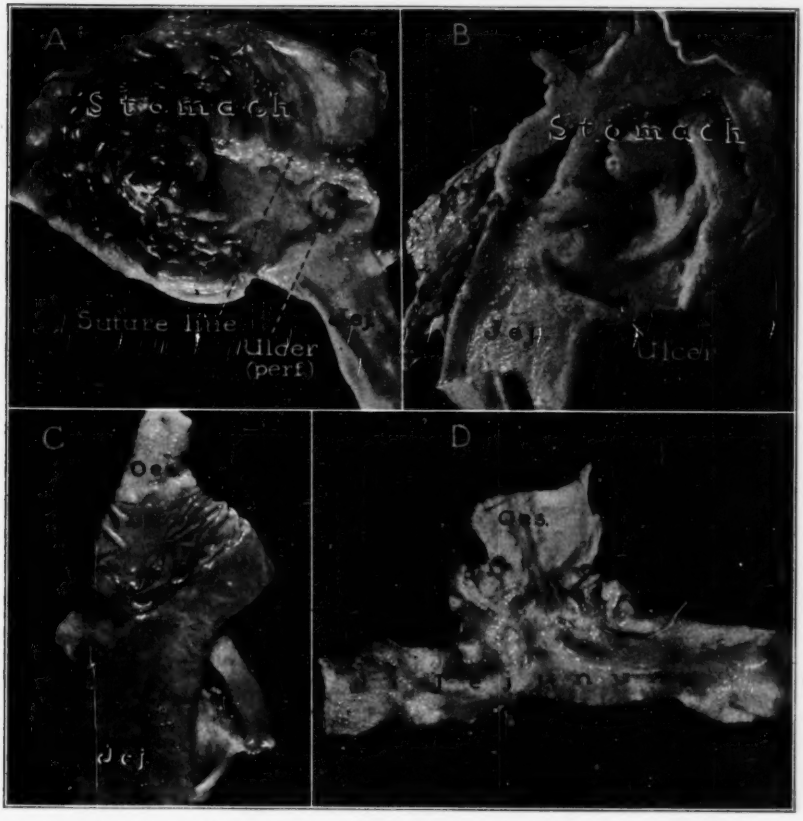


Fig. 3.—*A* and *B* represent autopsy specimen (dogs 3 and 1 respectively) revealing jejunal ulcers just distal to the suture line. In these animals three fourths of the stomach was removed, the stomach anastomosed to the jejunum as in figure 1 and a Mann-Williamson operation performed. *C* and *D* represent specimens removed from 2 animals (dogs 7 and 11 respectively) which underwent a "total" gastrectomy (except for a cuff 1 to 2 cm. wide) followed by a Mann-Williamson operation as shown in figure 2. No ulcer developed in any of the 8 animals. One of the animals (*C*) died one hundred and twenty days after operation because of inanition; another (*D*) was killed two hundred and twenty-three days after operation.

outline and measured 3 cm. by 8 mm. All the ulcers were situated in the jejunal mucosa a few millimeters distal to the anastomotic suture line. At death all animals showed an average of 35 per cent loss of preoperative body weight. The remnants of all stomachs appeared hypertrophied and dilated and, while not assuming their former size, showed a perceptible increase in volume.

*Series B.*—As stated previously, in this series a "total" gastrectomy was performed first, and after an interval of a few weeks to allow for recovery the operation for shunting the duodenal secretions into the terminal portion of the ileum was performed. At the second operation, in addition to the usual adhesions, in some instances the duodenum was

TABLE 2.—*Total Gastrectomy Followed by Diversion of Duodenal Secretions into the Terminal End of the Ileum*

| Dog | Weight, Lb. | Dates of Operations: Gastrectomy | Dates of Operations: Internal Duodenal Drainage | Date of Death | Survival Time, Days | Weight Loss, Lb. | Comment |
|---|---|---|---|---|---|---|---|
| 5 | 25 | 4/23/1947 | 5/ 9/1947 | 9/22/1947 | 134 | 12 | No jejunal ulcer; jejunitis |
| 6 | 25 | 4/25/1947 | 5/ 9/1947 | 11/21/1947 | 195 | 10 | No jejunal ulcer; severe jejunitis; mucosa intact |
| 7 | 19 | 5/ 2/1947 | 6/13/1947 | 10/10/1947 | 120 | 9 | No jejunal ulcer |
| 8 | 25 | 6/ 6/1947 | 8/ 3/1947 | 10/29/1947 | 87 | 10 | No jejunal ulcer |
| 9 | 20 | 8/29/1947 | 9/ 3/1947 | 10/20/1947 | 51 | 9 | No jejunal ulcer |
| 10 | 20 | 9/ 3/1947 | 9/17/1947 | 10/30/1947 | 44 | 7 | No jejunal ulcer |
| 11 | 21 | 3/19/1947 | 4/17/1947 | 11/25/1947 (killed) | 223+ | 9 | No jejunal ulcer; moderate degree of jejunitis; severe anemia |
| 12 | 23 | 3/22/1947 | 4/16/1947 | 11/25/1947 (killed) | 223+ | 10 | No jejunal ulcer; severe anemia |

found to be thickened and diffusely red, with mucosal hypertrophy. No hypertrophy or dilatation of the small amount of cardia was noted at this time. The jejunum did not show evidence of hypertrophy, dilatation or inflammation. It is possible that it was too early after the gastrectomy to note any changes in the gastrointestinal tract. The animals at this period had lost an average of 2 pounds (0.9 Kg.) in weight, or approximately 10 per cent of their preoperative body weight. The changes in the character of their stools were not unusually significant at this stage.

At death, after the two operations, all animals which survived thirty days or more showed marked evidence of nutritional imbalance, and some were extremely emaciated, with weight losses ranging from 40 to 50 per cent or more of their preoperative body weight (table 2). All animals consumed twice the amount of food necessary to maintain the body weight of a normal dog, yet the weight curve was downhill to an

extreme degree. The stools were large and voluminous, clay colored, soapy or putty-like in consistency and contained much undigested fat. No evidence of diarrhea or watery stool with admixture of blood was noted at any time.

At necropsy the complete absence of a gastric or jejunal stomal ulcer was noted in all experimental animals in this series. Further examination failed to reveal the presence of a possible healed ulcer. There was noted a slight dilatation of the jejunum opposite the remnant of gastric cardia, although the remnant did not appear dilated.

Microscopic sections of the cuff of cardia revealed the presence of oxyntic or acid parietal cells clearly up to the anatomic line of demarcation which marks the esophagogastric juncture. In this series of 8 experimental animals which survived the last operation for thirty days or more, death occurred in 6 animals forty-four, fifty-one, eighty-seven, one hundred and twenty, one hundred and thirty-four and one hundred and ninety-five days respectively after the second operation. At necropsy no stomal or jejunal ulcer was noted in the 6 animals; neither was there any evidence of a healed ulcer.

Two animals, nos. 10 and 11, were killed two hundred and twenty-three days after the second operation; no stomal ulcers were noted. The intestines in both animals were pigmented and of a deep buff color; all tissues and organs appeared extremely anemic.

I feel that the inclusion of additional food, particularly of the raw ground liver, in the diet played a significant role in keeping the animals alive. An incidental observation made during the course of this investigation revealed that if the raw ground liver was omitted from the diet, the downhill course of the animals was accelerated. Omission of the pancreas did not produce this effect.

## COMMENT

Our studies on the effect of "subtotal" and "total" gastrectomy on the development of a stomal ulcer when the duodenal, biliary and pancreatic secretions are diverted into the terminal portion of the ileum indicate that the presence of more than 2 or 3 per cent of secreting stomach is necessary in the pathogenesis of the stomal ulcer. As stated previously, the animals in which only three fourths of the stomach was removed (series A) lived for an average of only fifty-two days after operation and succumbed to the effects of a stomal ulcer and inanition. On the contrary, the animals in series B, although subjected to a total gastrectomy, with diversion of the duodenal secretions, survived an average of one hundred and twenty-five days. (This includes 2 animals killed two hundred and twenty-three days after operation.) No special atten-

tion was given these animals except for a modification of their diet as described previously.

The animals in both series were subjected to a diversion of duodenal, biliary and pancreatic secretions into the terminal portion of the ileum, but stomal ulcers developed only in those animals which had approximately 25 per cent of their stomach intact (series A), with the consequent presence of acid and pepsin in the alimentary tract. Can the failure of a stomal ulcer to develop in the animals in series B ("total" gastrectomy) be explained on the basis of an absence of the duodenal contents in the face of the fact that the animals in series A underwent the identical operation for shunting duodenal contents but had only three fourths of the stomach removed? Ulcers developed in all instances in the latter series. One is led to the obvious conclusion that the presence of acid and pepsin is necessary and complemental in the development of a stomal ulcer. One must, of course, consider the antiulcer factors in the bile, duodenal secretions and pancreatic secretions. Although alkalinity has previously been considered the most important of these factors, evidence is accumulating that there may be other factors in these secretions. At any rate, the antiulcer factor in the bile cannot be strong since obstruction of the common duct is not accompanied with a duodenal ulcer. However, when duodenal and pancreatic secretions are excluded from the intestinal tract (as in a pancreatoduodenectomy for carcinoma of the head of the pancreas) a jejunal ulcer will form in a high percentage of cases. It is obvious that an excess amount of acid is not the sole cause of the ulcer, since the animals in series A had three fourths of the stomach removed and stomal ulcers developed. It is also noted that in spite of the fact that vagotomy abolishes the cephalic phase of gastric secretion and the amount of acid secreted, in experiments previously reported [1] stomal ulcers developed in all animals subjected to a vagotomy and the Mann-Williamson operation. Can this failure of the jejunum to protect itself against the development of a stomal ulcer in spite of the presence of a minimal amount of acid and pepsin, as noted in our experiments, be explained only on the basis of increased jejunal susceptibility? True enough there is clinical evidence of the increased susceptibility of the distal portion of the small intestine to ulceration by acid (even in minimal amounts) in the perforation of ulcers in a Meckel diverticulum containing gastric mucosa. However, in the experiments herein reported the animals in both series were subjected to the same type of shunting operation diverting duodenal secretions into the ileum; the only difference in the two series of experiments was that in one series practically all the stomach was removed whereas in the other series one fourth of the stomach remained. It is, therefore, obvious that the presence of gastric secretions was the important factor in the cause of the ulcer.

## SUMMARY

In the 4 animals in series A in which three fourths of the stomach was extirpated and the continuity of the alimentary tract restored by an end to side gastrojejunostomy followed by diversion of the duodenal secretions (including bile and pancreatic juice) into the terminal portion of the ileum, stomal ulcers developed and they all died. The average duration of life in this series was fifty-two days. In 2 of the 4 animals the ulcer perforated.

These are contrasted with the 8 experimental animals in series B, in which a "total" gastrectomy was performed, with anastomosis of the gastric cardia to the jejunum followed by shunting of the duodenal secretions into the terminal portion of the ileum. In none of the animals in this series did a jejunal or stomal ulcer develop, and neither was there any suggestion of a healed stomal ulcer. Of the 8 animals in this series, 6 succumbed forty-four, fifty-one, eighty-seven, one hundred and twenty, one hundred and thirty-four and one hundred and ninety-five days after the second operation. Two animals (nos. 11 and 12) were killed two hundred and twenty-three days after operation. The average survival period for the animals in this group was one hundred and twenty-five days (including the 2 which were killed). All animals presented varying degrees of jejunitis, and the tissues appeared extremely anemic. The weight loss for the animals in this group averaged 45 per cent of their preoperative body weight. It is probable that with care the animals in series B could have lived indefinitely, but no particular attention was paid to their nutrition except for a modification of their stock diet.


## CONCLUSION

From these data it is concluded that the presence of gastric secretion is the important factor in the development of an ulcer after a Mann-Williamson operation has been performed, so far as no ulcer will develop if all (at least 98 per cent) of the stomach is removed.

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# EFFECTS OF VAGOTOMY IN THE RAT

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STUDIES concerning the effects of section of the vagi are numerous and date back to the sixteenth century. In 1883, on the basis of his own experiments and from an extensive review of previous literature, Heidenhain [1] emphasized that bilateral vagotomy performed in the neck was inevitably fatal, yet when done below the diaphragm it appeared to be a rather harmless operation. It remained, however, according to Pavlov,[2] for Krehl [3] in Ludwig's laboratory to evaluate properly the effect of double vagotomy on survival time. He clearly established that animals can survive bilateral section of the vagus below the lung root but invariably succumb after such section in the neck. Later experiments on dogs, cats and rabbits [4] and the more recent ones of Ferguson [5] on monkeys amply confirmed the results of these investigators. No generally acceptable explanation is, however, as yet available for the fact that this operation, when performed in the neck, is inevitably

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1. Heidenhain, R.: Physiologie der Absonderungsvorgänge, in Hermann's Handbuch d. Physiologie, Leipzig, F. C. W. Vogel, 1883, pt. 1, chap. 5, p. 1.

2. Pavloff, I. P.: On the Death of the Animals after Section of Nervi Vagi, Proc. Soc. Russian Physicians, St. Petersburg, April 1895, vol. 61; On Survival of Vagotomized Dogs, ibid. March-June, vol. 63; Experimental Therapy as a New and Extremely Fruitful Method of Physiological Investigations, in Congrès International de Médicine, Paris, Aug. 2-9, 1900, Paris, 1901.

3. Krehl, R.: Ueber die Folgen der Vagusdurchschneidung, Arch. f. Physiol. u. Anat., 1892, p. 278.

4. McCrea, E. D.: The Nerves of the Stomach and their Relation to Surgery, Brit. J. Surg. **13**:621, 1926. McCrea, E. D.; McSwiney, B. A., and Stopford, J. S. B.: The Effect on the Stomach of Secretion of Vagi Nerves, Am. J. Exper. Physiol. **16**:195, 1926.

5. Ferguson, J. H.: Effects of Vagotomy on the Gastric Functions of Monkeys, Surg., Gynec. & Obst. **62**:689, 1936.

fatal unless extraordinary measures are applied.[6] Pavlov's school holds that of the numerous effects of vagotomy believed to be the cause of death following bilateral section in the neck the most important and hardest to control is the pronounced impairment of the functions of the digestive system. This results from the elimination of the nervous control of gastric, pancreatic and possibly also intestinal secretions plus impairment of motility of the esophagus and stomach, which lead to inadequate digestion and nutrition. When the effects (stagnation, putrefaction of food in the stomach and esophagus and aspiration pneumonia) of these altered functions were allayed through specific measures, Pavlov found that dogs vagotomized at any level could be made to survive indefinitely. These measures could be applied only if the animals were esophagotomized and provided with a gastric fistula.

Pavlov and his associates, as well as some of their predecessors, attributed better survival of animals vagotomized below the lung root to the anatomic difficulties in achieving complete vagotomy at this level. Aside from the difficulty of severing all free vagal fibers below the lung root, the entrance of some vagal branches above this level into the esophageal wall and their passage through it to the stomach were thought to be highly probable. These factors would make complete severance of all vagal fibers at this level well nigh impossible. Only complete and consistent absence of acid gastric secretion in response to sham feeding in repeated trials could, according to Pavlov, be accepted as conclusive evidence of complete severance of vagal innervation to the stomach.

It is not our purpose in this paper to review clinical experiences in bilateral vagotomy, but there appears to be a sharp difference of opinion regarding the possibility—in man, too—of achieving complete severance of all vagus fibers below the lung root. Some[7] are in agreement with the view regarding the anatomic difficulties expressed by Pavlov. Others[8] believe that complete severance of all vagal fibers at this level can be effectively accomplished.

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6. Yurgens, N. P.: The Condition of the Digestive Tract in Chronic Paralysis of the Vagus Nerves, Thesis, St. Petersburg, P. I. Schmidt, 1892. Kachkovsky, P.: On Survival of Dogs After Simultaneous Section of Cervical Sympathetics, Thesis, St. Petersburg, Trink & Fyusno, 1899. Cheshkov, A. M.: One Year and Seven Months' Survival of a Dog after Double Vagotomy in the Neck, Thesis, St. Petersburg, P. P. Soïkin, 1902. Pavloff.[2]

7. Weinstein, V. A.; Colp, R.; Hollander, F., and Jemerin, E. E.: Vagotomy in the Therapy of Peptic Ulcer, Surg., Gynec. & Obst. **79**:297, 1944. Bradley, W. F.; Small, J. T.; Wilson, J. W., and Walter, W.: Anatomic Considerations of Gastric Neurectomy, J. A. M. A. **133**:459 (Feb. 15) 1947. Miller, E. M., and Davis, C. B., Jr.: An Anatomic Study of the Vagus Nerves, ibid. **133**:461 (Feb. 15) 1947.

8. Dragstedt, L. R., and Owens, F. M., Jr.: Supradiaphragmatic Section of Vagus Nerves in Treatment of Duodenal Ulcers, Proc. Soc. Exper. Biol. & Med.

*(Footnote continued on next page)*

The rather recent extensive application of bilateral resection of the vagus to the treatment of gastric and duodenal ulcer makes a more complete experimental study of the manifold effects of this operation imperative.

To the best of our knowledge, no observations have been reported concerning the effects of vagotomy on rats. Our primary interest in this problem was to establish the role of the vagi in interdigestive gastric secretion. In addition, we were also concerned with the possible effects of vagotomy on the motor functions of the gastrointestinal tract and on the nutrition and well-being of the animals. The rat is especially valuable for such investigations since it is widely used in nutrition studies and its stomach has recently been shown to be so readily the site of true peptic ulceration.[9]

## EXPERIMENTS

*The Technic of Vagotomy.*—Wistar strain rats, chiefly male, weighing 150 to 180 Gm., which had been grown in our own colony were subjected to transdiaphragmatic resection of the vagus nerve. The following technic was used:

The animal is anesthetized with ether and placed on its right side. An incision 1 to 1½ inches (2.54 to 3.81 cm.) long, beginning at the linea parasternalis, is made on the left side of the abdomen 3 to 5 mm. below the ribs. Urethane (0.9 cc. of 10 per cent solution per hundred grams of weight) is injected into the cecum, and the stomach and spleen are withdrawn. After the left lobe of the liver is displaced to the right, the esophagus is clearly exposed and the vagus trunks, both right and left (actually lying somewhat anteriorly and posteriorly respectively), can be seen as well as a plexus formation about midway between the diaphragm and the cardia. Each trunk just above the plexus is lifted from the esophagus with a fine forceps and isolated with a fine hook, damage to the blood vessels being avoided. In order to achieve vagus resection, each vagus nerve trunk is pulled downward into the abdomen

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**53**:152, 1943. Dragstedt, L. R., and Schafer, P. W.: Removal of Vagus Innervation of Stomach in Gastro-Duodenal Ulcer, Surgery **17**:742, 1945. Dragstedt, L. R.; Palmer, W. L.; Schafer, P. W., and Hodges, P. C.: Supradiaphragmatic Section of Vagus Nerves in Treatment of Duodenal and Gastric Ulcers, Gastroenterology **3**:450, 1944. Moore, F. D.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: Transdiaphragmatic Resection of the Vagus Nerves for Peptic Ulcer, New England J. Med. **234**:241, 1946; Resection of the Vagus Nerves in Peptic Ulcer, J. A. M. A. **133**:741 (March 15) 1947. Grimson, K. S.; Baylin, G. J.; Taylor, H. M.; Hesser, F. H., and Rundles, R. W.: Transthoracic Vagotomy, ibid. **134**:925 (July 12) 1947.

9. Shay, H.; Komarov, S. A.; Fels, S. S.; Meranze, D.; Gruenstein, M., and Siplet, H.: A Simple Method for the Uniform Production of Gastric Ulceration in the Rat, Gastroenterology **5**:43, 1945.

as far as possible, and the longest possible segment (never less than 1 cm.) is excised from the level of the diaphragm to the cardia. After proper resection, the upper stump should, at biopsy or autopsy, be found in the thoracic cavity, 7 to 10 mm. above the diaphragm. In about 90 per cent of the rats, two single vagal trunks emerge beneath the diaphragm. Occasionally, one or two additional small branches also emerge. They can be detected later at autopsy only by careful examination through a magnifying glass. These branches, therefore, may escape resection. In cases of incomplete vagotomy the effects on gastric secretion, motility and survival are strikingly different from those following complete vagotomy.

After the resection of the nerves is completed, the organs are replaced in the abdominal cavity and the wound is closed in the usual manner.

Operations performed in addition to vagotomy, depending on the type of experiment, included pyloric ligation, production of a gastric fistula, exteriorization of a portion of the cecal wall and esophagotomy.

*The Effects of Vagotomy on Spontaneous Gastric Secretion.*—Rats were fasted for a period long enough for previously ingested food to be completely digested and absorbed (eighteen to seventy-two hours), with water allowed ad libitum. They exhibited a considerable spontaneous secretion of gastric juice which had a composition similar to that induced by sham feeding. Acidity, pepsin content and rate of this secretion depended to a large extent on the conditions of the experiment; in unanesthetized animals this "interdigestive secretion" was greater in amount and was rather labile when compared with that of the anesthetized animals. The rate of secretion was influenced by the depth of anesthesia. These observations alone indicate the importance of the nervous mechanism in this phase of gastric secretion. That parasympathetic innervation is especially concerned is evidenced by the effect of atropinization on the secretion.[10]

Friedman[11] reported that spontaneous secretion in the rat is not affected by atropine, but we have found that sufficiently large doses of atropine did inhibit it almost completely. However, the effects of atropine are manifold, and the dosage required to cause marked inhibition was so large that more direct experiments were necessary to establish the exact role of the vagi in controlling spontaneous secretion in rats.

10. Komarov, S. A.; Shay, H.; Rayport, M., and Fels, S. S.: Some Observations on Gastric Secretion in Normal Rats, Gastroenterology, **3**:406, 1944.

11. Friedman, M. H. F.: Histamine Ineffective in the Rat as a Gastric Secretory Stimulant, Proc. Soc. Exper. Biol. & Med. **54**:42, 1943.

We have studied the immediate and remote effects of both complete and partial vagotomy.

*The Immediate Effects of Vagotomy on Gastric Secretion.*—Two technics were employed in studying the immediate effects. One had the advantages of simplicity and minimum surgical trauma since, in addition to vagotomy, it involved only pyloric ligation and exposure of the cecum. This procedure did not, however, prevent contamination of the gastric juice by saliva or other extraneous matter (feces or hair). Such contamination was avoided in the second method, which included esophagotomy in addition to the aforementioned procedures.

*Experiments with Simple Pyloric Ligation.*—The technic employed is similar to that previously described for the experimental production of gastric ulceration in rats.[9]

Animals weighing 150 to 180 Gm. are fasted for forty-eight hours but allowed water ad libitum. They are anesthetized with ether. Through a midline incision 5 to 8 mm. long below the umbilicus, a small portion of the cecal wall is exteriorized and urethane injected. Then through a left subcostal incision 3 to 4 cm. in length one or both vagi are resected as described previously, and the pylorus is ligated. The wound is sutured, and the animals are left in clean cages overnight for seventeen to nineteen hours. They are then anesthetized by the intracecal injection of pentobarbital sodium and killed. The abdomen is opened and a ligature placed around the esophagus. The stomach is removed, and its contents are drained into a graduated centrifuge tube through a nick in the wall of the stomach along the greater curvature proximal to the pyloric ligature. The contents of each stomach were individually analyzed as described in the following paragraphs.

*Analysis of Gastric Contents.*—The specimens were centrifuged in a graduated centrifuge tube at 2,000 revolutions per minute for ten minutes and the respective volumes of supernatant and solid materials recorded. The rate of secretion is expressed in cubic centimeters per hour per hundred grams of body weight, which was calculated from the volume of supernatant fluid. The supernatant fluid was pipetted off and the hydrogen ion concentration, free and total acid, total chlorides and pepsin were determined by routine methods used in this laboratory.[12]

Groups of 4 to 6 animals were used for each experiment. Controls were included in each group. Control animals were treated exactly like the vagotomized animals except that their vagi were "handled" but not sectioned.

The results showing only mean values are presented in table 1. The results are so unequivocal that no elaborate statistical analysis appears necessary.

12. Komarov and others.[10] Shay and others.[9]

Bilateral vagotomy produced an average reduction in the rate of secretion to 41 per cent of that in the controls, while unilateral vagotomy reduced it to 78 per cent. It is noteworthy that in no animal subjected to bilateral vagotomy was free acid present in the stomach. The relatively low figures for total chloride in the gastric contents of animals which underwent unilateral and, particularly, bilateral vagotomy indicated a considerable contamination of the gastric contents with saliva and that such contamination was proportionately greater in animals subjected to bilateral vagotomy than in those subjected to resection of one vagus nerve. This is probably due to the greater reduction in gastric secretion in the former, since it is not likely that these animals swallowed more saliva than the latter.

TABLE 1.—*Immediate Effect of Vagotomy on Gastric Secretion (Animals Not Subjected to Esophagotomy)*

| | Control | Vagotomy | | |
|---|---|---|---|---|
| | | Single | | |
| | ↓ | Left | Right | Double |
| Number of animals | 20 | 15 | 16 | 15 |
| Rate, ml./hr./100 Gm. | 0.265 | 0.217 | 0.198 | 0.109 |
| *pH* | 1.76 | 1.83 | 1.80 | 3.89 |
| Acidity, mEq./liter | | | | |
| Total | 77 | 73 | 79 | 31 |
| Free | 31 | 25 | 27 | 0 |
| Chloride, mEq./liter | 148 | 133 | 145 | 110 |
| Pepsin, Mett units | 189 | 145 | 180 | 107 |

Results produced by the section of one vagus nerve were essentially the same whether the left or right nerve was severed.

*Experiments with Pyloric Ligature and Esophagotomy.*—The experimental technic used in this group was the same as that used in the preceding series except that after exteriorization of a small portion of the cecal wall and injection of urethane esophagotomy was performed. The esophagus was exposed by an incision 1 cm. long just above the sternum, slightly to the left of the midline, ligated with a fine thread as far aborally as possible and cut just above the ligature. The proximal end of the cut esophagus was sutured into the upper end of the incision and the rest of the wound closed. Only then were the vagi resected and the pylorus ligated.

Esophagotomy increases the operative time only about five minutes. While additional trauma in a highly sensitive region undoubtedly aggravated operative shock, it did not inhibit spontaneous secretion in the control animals. This can be seen by comparing the results in table 1 with those in table 2. The number of experiments in this group was

not so large as in the previous one, since individual variations in this series were even less notable than in the first.

Figures for total chloride (table 2) indicate that the gastric juice was only slightly contaminated, if at all, so that the results observed reflect the actual secretory activity of the stomach. Bilateral vagotomy abolished secretion so nearly completely that sufficient gastric contents were not available for complete analysis; only the rate of secretion and the $p_H$ could be determined in each animal, while only a few scattered determinations were possible on acidity and chloride and none on pepsin.

Again results produced by resection of the vagus on the right or left side were practically identical. Unilateral vagotomy reduced the rate of secretion to about one third and the output of free acid to approximately one fourth of the control values without otherwise materially altering the composition of the secretion. These changes were accompanied with

TABLE 2.—*Immediate Effect of Vagotomy on Gastric Secretion (Animals Subjected to Esophagotomy)*

| | | Vagotomy | | |
|---|---|---|---|---|
| | | Single | | |
| | Control | Left | Right | Double |
| Number of animals | 9 | 6 | 7 | 7 |
| Rate, cc./hr./100 Gm. | 0.244 | 0.082 | 0.085 | <0.01 |
| $p_H$ | 1.24 | 1.42 | 1.41 | 2.74 |
| Acidity, mEq./liter | | | | |
| Total | 99 | 92 | 96 | 85 |
| Free | 77 | 55 | 51 | 30 |
| Chloride, mEq./liter | 150 | 148 | 154 | 153 |
| Pepsin, Mett units | 205 | 258 | 208 | Quantity not sufficient |

a correspondingly higher $p_H$ in the secretion of the vagotomized animals. Some increase in the pepsin content of the animals subjected to section of the left vagus nerve does not appear significant.

These results indicate that unilateral vagotomy depressed the rate of secretion considerably while bilateral vagotomy inhibited gastric secretion completely, or nearly so. The small amounts of gastric juice (0.1 to 0.2 cc.) recovered from the group subjected to the latter at the end of the eighteen hour period could represent secretion remaining in the stomach at the time of pyloric ligation.

The most striking difference between the results in animals which were subjected to esophagotomy and in those which were not was the failure of bilateral vagotomy to abolish gastric secretion in the latter series. This may be due to the gastric secretogogue action of saliva in these animals, since Sokolov [18] showed such an action for saliva when

13. Sokolov, A. P.: Analysis of the Secretory Action of the Stomach in the Dog, Thesis, St. Petersburg, F. Vaïsberg and P. Gershunin, 1904.

it is introduced into the whole, isolated stomach, and Savich and Zeljony [14] demonstrated that sodium carbonate, a constituent of saliva, excites gastric secretion when placed in contact with pyloric mucosa. Our results indicate that, in the rat, saliva may act as a secretogogue in the absence of vagal innervation.

### THE EFFECTS OF ACUTE VAGOTOMY ON FORMATION OF ULCER

Normal animals subjected to pyloric ligation when the stomach is empty always develop extensive gastric ulceration,[9] which is mostly confined to the rumen and, to a lesser degree, also involves the body and antrum of the stomach. In all control animals severe ulcerations developed; some had so many it was impossible to count them. Nine animals comprising the control group (table 2) had several hundred ulcerations, many of them perforated. Of 13 animals subjected to unilateral vagotomy, 6 had no ulcers and the remaining 7 had eight tiny ulcerations in all, of which six were located in the rumen. No ulcerations were found in the animals subjected to bilateral vagotomy, while ulceration was much less pronounced in those in which one vagus nerve was resected than in the control animals. The results in the animals which underwent complete vagotomy are readily explained by the almost complete absence of secretion in the stomach. Although the number of ulcers were not counted as thoroughly in the groups represented in table 1, similar results were observed.

### REMOTE EFFECTS OF VAGOTOMY ON GASTRIC SECRETION

At first we experienced difficulties in keeping completely vagotomized rats alive longer than three or four days. The animals withstood the operation well, taking water and milk the first day postoperatively. On the second or third day they appeared vigorous and eagerly ate solid food. When placed on our diet of purina checkers,[9] they refused food on the third or fourth day postoperatively and soon died, none surviving more than a week. At autopsy the stomachs of all these animals were found distended with large masses of food. The esophagus was also full of food, as well as the mouth cavity and the nostrils, and occasionally food particles were found in the trachea. However, the small intestine was empty of chyme, and little feces was present in the cecum and colon. Evidently gastric secretory and motor functions were so impaired that adequate digestion was not possible. While searching for a solution to this nutritional problem, we lost more than 50 vagotomized animals. Suffice it to mention here that by using a diet consisting

14. Savich, V., and Zeljony, G.: Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. **150**:128, 1913.

in part of predigested food, we maintained completely vagotomized animals in reasonably good condition for many weeks, the longest period of survival being one hundred and twenty days for 1 animal at the time it was killed.

In these experiments we also employed two technics. In one series the effects of vagotomy on gastric secretion were studied after pyloric ligation alone. In the other the animals were esophagotomized and both gastric and cecal fistulas were made in addition to ligation of the pylorus.

In the first series 3 groups of animals were studied: control animals, those subjected to incomplete vagotomy and those subjected to complete vagotomy. Incomplete vagotomy occurred by accident rather than by design. In some animals the vagal trunks were so well developed that we decided not to destroy the esophageal plexus and only excised the usual length of the trunks. Subsequent autopsies on these animals disclosed well developed neuromas (3 to 7 mm.) at the proximal end of the divided nerve as well as definite strands of nerve tissue extending from the neuromas toward the stomach. In other animals a small branch of the vagus, usually on the right side of the esophagus, escaped detection during the operation and was not excised. In the "complete vagotomy" group, all visible fibers of the esophageal plexus were excised in addition to resection of both vagal trunks, and no uncut fibers or signs of regeneration were found at autopsy. All vagotomized animals accumulated hair in the stomach. This was removed through a small incision in the rumen at the beginning of the period of starvation, forty-eight hours before the actual experiment. On the day of the experiment the pylorus was ligated through the usual midline incision, with the animals under ether anesthesia. The animals recovered from the anesthesia almost immediately after the wound was closed. They were killed six hours after pyloric ligation, and the gastric contents were collected as described previously.

The results obtained with this technic are given in table 3; they closely resemble those obtained in the experiments testing the immediate effects of acute vagotomy on animals not subjected to esophagotomy. Complete vagotomy performed twelve to twenty-nine days before the experiment resulted in a decrease in the rate of secretion to about one third, in the output of total acid to approximately one eleventh and in pepsin output to about one fourth of that of the control animals. There was a decrease in the amount of free acid to zero. Incomplete vagotomy performed eighteen to thirty-eight days before testing also produced a striking decrease in gastric secretion: diminution of the rate to about one half and a considerable lowering of acidity, especially

of free acid. The change, however, was not as striking as that following complete vagotomy. Low figures for total chloride in the completely vagotomized group suggest considerable contamination of the gastric contents with saliva. This may, also in these experiments, be partly responsible for the relatively high secretion.

Esophagotomy and the production of gastric and cecal fistulas, in addition to pyloric ligation, were employed in a number of animals surviving complete vagotomy for periods of from twelve to one hundred

TABLE 3.—*Remote Effect of Vagotomy on Gastric Secretion (Animals Subjected to Pyloric Ligature Only)*

| Days Post-operatively | Weight Gain, Gm./Day | Rate, Cc./Hr./100 Gm. | *pH* | Acidity MEq./Liter Total | Acidity MEq./Liter Free | Chloride, MEq./Liter | Pepsin, Mett Units | Hair, Cc./Day |
|---|---|---|---|---|---|---|---|---|
| | | | | Control | | | | |
| 19 | +0.42 | 0.81 | 1.18 | 105 | 72 | 157 | 100 | None |
| 19 | +0.21 | 0.52 | 1.17 | 100 | 74 | 152 | 77 | None |
| 19 | +1.10 | 1.04 | 1.12 | 113 | 82 | 156 | 154 | None |
| 29 | +0.55 | 0.71 | 1.22 | 106 | 69 | 147 | 36 | None |
| 29 | +1.00 | 0.93 | 1.18 | 121 | 73 | 155 | 52 | None |
| Mean | | 0.80 | 1.17 | 109 | 74 | 153 | 84 | None |
| Mean output* | | .... | .... | 87 | 59 | ... | 67 | None |
| | | | | Incomplete Vagotomy | | | | |
| 29 | −0.60 | 0.30 | 2.81 | 68 | 0 | 150 | 135 | 0.035 |
| 36 | −0.22 | 0.58 | 1.49 | 78 | 35 | 152 | 196 | 0.083 |
| 38 | 0 | 0.34 | 3.53 | 68 | 0 | 163 | 207 | 0.079 |
| 18 | −1.80 | 0.34 | 1.74 | 90 | 24 | 161 | 353 | 0.050 |
| Mean | | 0.39 | 2.03 | 76 | 15 | ... | 223 | ..... |
| Mean output | | .... | .... | 30 | 6 | ... | 87 | ..... |
| | | | | Complete Vagotomy | | | | |
| 12 | −3.30 | 0.27 | 4.68 | 28 | 0 | 100 | 31 | 0.080 |
| 12 | −4.00 | 0.34 | 7.08 | 0 | 0 | 120 | 8 | 0.060 |
| 12 | −4.80 | 0.27 | 3.87 | 46 | 0 | 133 | 85 | 0.040 |
| 12 | −2.80 | 0.23 | 3.07 | 42 | 0 | 144 | 108 | 0.070 |
| 29 | −2.00 | 0.19 | 3.51 | 44 | 0 | ... | 125 | 0.024 |
| Mean | | 0.26 | 3.66 | 32 | 0 | 126 | 71 | ..... |
| Mean output | | .... | .... | 8 | 0 | ... | 19 | ..... |

* Mean output indicates acidity expressed as milliequivalents per hour per hundred grams and pepsin expressed as Mett units per hour per hundred grams.

and six days and in a corresponding number of control animals. It was necessary in vagotomized animals surviving for more than a month to remove balls of accumulated hair surgically through a small incision in the rumen. This procedure had to be repeated every three to four weeks. Control animals were treated similarly, although no hair was present in the stomach. In each of these animals a gastric fistula was made and the cecum partially exteriorized about one week before the experiment. The animals were starved twenty-four or forty-eight hours before esophagotomy was performed; with the animals under urethane anesthesia the pylorus was tied and gastric secretion was collected for

sixteen to twenty-four hours. Some of them were trained to stand handling without anesthesia and were subjected to sham feeding experiments. The results are summarized in table 4.

This table indicates that the rate of spontaneous gastric secretion in animals surviving complete vagotomy from twelve to one hundred and six days was reduced to about one fourth that in control animals and free acidity was approximately 10 per cent lower, with corresponding changes in $p_H$. Sham feeding produced no effect in the vagotomized rats, while the stomachs of control animals responded with characteristically increased secretion.

It will be noted that in these series the rate of secretion was considerably lower in both vagotomized and control animals (table 4) than in those animals in which pyloric ligation only had been used

TABLE 4.—*Remote Effect of Vagotomy on Gastric Secretion (Animals Subjected to Esophagotomy, Pyloric Ligature and Gastric and Cecal Fistula)*

| | Number of Animals | Rate, Cc./Hr./ 100 Gm. | $p_H$ | Acidity MEq./Liter Total | Acidity MEq./Liter Free | Chloride, MEq./ Liter | Pepsin, Mett Units |
|---|---|---|---|---|---|---|---|
| A. Interdigestive Phase | | | | | | | |
| Control..... | 10 | 0.156 | 1.49 | 84 | 46 | 152 | 180 |
| Vagotomy..... | 13 | 0.039 | 2.08 | 97 | 41 | ... | ... |
| B. Sham Feeding Phase | | | | | | | |
| Control | | | | | | | |
| C *..... | 2 | 0.090 | 2.11 | 40 | 25 | ... | ... |
| SHF †..... | | 0.270 | 1.51 | 64 | 39 | ... | 452 |
| Vagotomy | | | | | | | |
| C *..... | 5 | 0.032 | 2.23 | .. | .. | ... | ... |
| SHF †..... | | 0.030 | 2.27 | .. | .. | ... | ... |

* C indicates control period.
† SHF indicates sham feeding period.

(table 3). The higher rate of secretion in the latter group may be due either to less operative shock or to stimulation by saliva or both. The following conclusions concerning the effects of vagotomy on the spontaneous or "interdigestive phase" of gastric secretion in rats are, we believe, justified:

1. Acute complete vagotomy abolishes spontaneous secretion. Unilateral vagotomy inhibits it considerably, especially if entrance into the stomach of extraneous materials is prevented by esophagotomy.

2. Some restoration of spontaneous secretion occurs in animals surviving complete vagotomy for several weeks, but this secretion is exceedingly small and is probably produced by a humoral mechanism, since it is not affected by sham feeding. Incomplete vagotomy also produces a considerable reduction of spontaneous secretion.

## OTHER REMOTE EFFECTS OF COMPLETE BILATERAL VAGOTOMY

*Conditions for Survival.*—We stated previously that completely vagotomized rats do not survive more than a week when placed on a diet of purina checkers,® powdered or whole.

The addition of choline hydrochloride to the drinking water prolonged the survival time of vagotomized rats on a purina® diet to as long as three weeks if each animal consumed 100 to 150 mg. (50 to 100 mg. per hundred grams of body weight) of the drug daily. This dosage proved to be toxic. The animals frequently became cyanotic and apparently suffered intestinal cramps. They did not thrive and lost weight. At biopsy or autopsy the accumulation of solids in the stomach was not so pronounced as in animals kept on the same diet without choline (fig. 2).

Only if the diet contained predigested proteins as a source of nitrogen and starch or sucrose as carbohydrate was it possible to keep vagotomized animals alive indefinitely. Starch was found to be superior to sucrose since it permitted the animals to keep themselves clean more easily and so prevented a too rapid accumulation of hair in the stomach. The final experimental diet used was as follows:

| | |
|---|---|
| Liver powder (Wilson) | 4% |
| Lactamin® (protein hydrolysate) | 30% |
| Crisco® | 8% |
| Salts (Steenboch)[15] | 4% |
| Vitamins A and D (natural vitamin oil) | 2% |
| Corn oil (Mazola) | 2% |
| B Plex® (Wyeth) | 2% |
| Corn starch | 48% |
| Vitamin K | 10 mg. per thousand grams of diet |

## OTHER ABNORMALITIES IN THE DIGESTIVE TRACT FOLLOWING BILATERAL VAGOTOMY

The esophagus below the lung root was always enlarged, even when empty. While in the control animals its diameter was about 2 mm., in completely vagotomized animals it was always more than 5 mm. when empty and even wider when filled with air, saliva or gastric juice. When the esophagus was filled with food masses, it was occasionally as large as 10 mm. in diameter. In some cases the esophagus was distended even in the neck. It was frequently filled with food in living animals. In addition, completely vagotomized animals readily tended to regurgitate gastric contents into the mouth cavity. This phenomenon was never observed in normal rats. Transit of food through the esophagus was apparently also disturbed, since the esophagus of many vagotomized rats at autopsy was filled with well masticated food masses which were alkaline in reaction. By contrast with the esophagus, the cardia appeared constricted. Actually this was not so, since in most

15. Steenboch, H., and Nelson, E. M.: Fat Soluble Vitamins: XIII. Light in its Relation to Ophthalmia and Growth, J. Biol. Chem. **56**:355, 1923.

cases the diameter of the cardia was 2.5 mm., while in the control animals it measured 2 mm. The function of the cardia, however, appeared to be impaired. Its appearance suggested a state of fixed incomplete closure. On biopsy, the stomach was always found to be much larger than normal and flabby in appearance even when it was empty. The pylorus nearly always appeared contracted. The small intestines of animals which had succumbed without being subjected to experimentation contained little or no chyme, even if the stomach contained food, and the frequent occurrence of neutral or alkaline reaction in the intestines—a phenomenon observed in few normal animals—was striking. At all biopsies or autopsies the cecum and colon contained little feces.

These findings indicate a severe impairment of the motor functions of the esophagus, cardia, stomach and pylorus. Changes in the

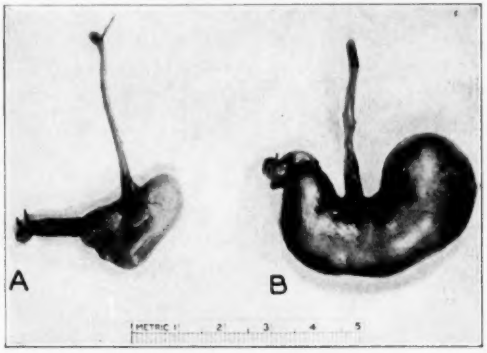


Fig. 1.—*A*, stomach and esophagus of control animal on colony diet of purina checkers—forty-eight hours of starvation except for water before being killed. *B*, stomach and esophagus of animal after bilateral transdiaphragmatic vagotomy. Animal maintained on colony diet of purina checkers for five days followed by forty-eight hours of starvation before being killed. Note the empty appearance of the stomach of the control animal in contrast to the distended stomach of the vagotomized animal. The reason for the distention is seen in the large food mass in the opened stomach in figure 2. Both animals were the same age and weight.

intestines may or may not be secondary—at present we have no basis on which to form any definite conclusions. The accompanying photographs illustrate some of the changes.

It should be added that the incidence of pathologic changes in the lungs was high in vagotomized animals. Many autopsies showed spotty congestion and hemorrhagic infiltration of both lungs, which in most cases was confined chiefly to the lower lobes. In some cases both lungs appeared to be diffusely infiltrated. Such abnormalities were not observed in the control animals.

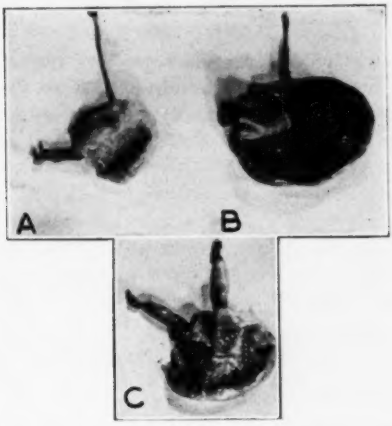


Fig. 2.—Stomach laid open after incision along greater curvature. Weights of animals, 120 Gm. ± 10 Gm. *A*, same as in figure 1. Stomach completely empty. *B*, same as in figure 1. The large mass of food explains the distended appearance in figure 1. *C*, same as in *B*, except that animal received choline, 50 mg. per hundred grams of body weight daily, from the day of vagotomy. The improved motor function of the stomach over that of *B* is apparent.

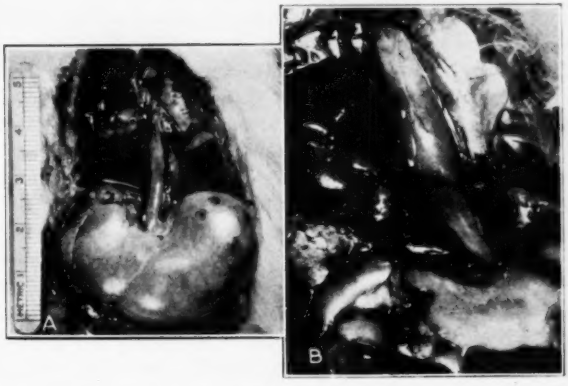


Fig. 3.—*A*, control animal, with vagi intact, after forty-eight hours of starvation. Esophageal fistula in neck; pylorus ligated. Animal was killed nineteen hours after pyloric ligation. Note the usual result after such procedure. The stomach is distended with gastric secretion, and typical ulcerated areas are visible in the rumen through the serosal surface. *B*, same procedures as in control animal in *A* except that this animal had bilateral transdiaphragmatic vagotomy done one hundred and five days previously. Note the collapsed state of the stomach, which obviously had secreted little gastric juice in the nineteen hour period following pyloric ligation. In spite of the small quantity of gastric secretion, note the dilatation of the entire esophagus and the relatively narrowed appearance of the cardia.

### NUTRITION

The partially predigested diet which we were forced to use in these experiments did not appear to be as adequate as we should have liked. Although the control animals gained weight steadily, their rate of increase was much less than that obtained in normal rats of the same age on our house diet. Furthermore, their fur did not remain as smooth as that of animals on a completely satisfactory diet. Vagotomized animals on the experimental diet as a rule lost weight or only barely maintained it, while few showed any gain in weight (table 3). These results indicate that the profound changes incident to complete vagotomy interfere with the proper utilization of even predigested food.

Studies conducted on the rat with Dr. R. Kolm and Dr. L. Edwards, to be detailed elsewhere, show the digestion and absorption of fats and the storage of glycogen by the liver to be unaffected by complete vagotomy.

### COMMENT

Our results show that the immediate effect of bilateral transdiaphragmatic vagotomy in the rat is almost complete cessation of spontaneous gastric secretion. McCrea and his associates [4] have ascribed certain other immediate effects of bilateral vagotomy on gastric motility to the narcosis and shock incidental to vagotomy and not to the severance of vagal innervation. Such a mechanism cannot be held responsible for the inhibition of gastric secretion in our experiments since (1) control animals were treated exactly as the vagotomized animals in every detail except that vagotomy was not performed and (2) inhibition of secretion was permanent as long as the animals were allowed to survive. The results of our experiments on rats are in good agreement with those of Pavlov and his associates on dogs, in which the function of the vagi as the true secretory nerves for the gastric glands was first established. An analysis of our data, furthermore, places the mechanism of spontaneous gastric secretion in the unanesthetized fasting rat almost completely under nervous (vagus) control, with the possibility that humoral factors may contribute a small part in the mechanism of this secretion. The constant presence of bile in the intestine of the rat, as previously mentioned,[10] may be responsible, at least in part, for the humoral part of the mechanism.

Unilateral vagotomy in the rat produced results which forced us to conclusions that are in sharp contrast with the view expressed by many investigators that partial vagotomy fails to influence gastric secretion or only causes some initial inhibition followed by complete restoration of secretory function. In the rat, incomplete vagotomy is followed by a substantial and persistent decrease in the rate and acidity of spontaneous secretion. These changes promptly follow the operation and render a

high degree of protection against ulceration following pyloric ligation under conditions which produce uniform ulceration in animals with both vagi intact.

Finally we would emphasize the fact that a truly complete vagotomy below the lung root in the rat is a fatal operation unless extraordinary measures are taken to enable the animals to survive. They can survive for a long period if a special diet is used which overcomes the decided impairment of gastric motor function. Even when this is accomplished, the vagotomized rats never become completely healthy animals but remain "invalid," the term used by Pavlov [2] in his vivid description of vagotomized dogs.

Both the great difficulties Pavlov encountered in keeping completely vagotomized dogs alive and the identical hazards we observed in rats following such an operation caused us to question the completeness of vagotomy in those clinical studies reporting the operation to be fraught with no serious consequences.

## SUMMARY

Studies on gastric secretion, motility and nutrition were conducted on more than 200 vagotomized rats. Resection of more than 1 cm. from each vagal trunk was performed below the diaphragm through a left subcostal incision; the upper limit of this resection actually extended into the thoracic cavity for 5 to 10 mm., since the nerves were pulled aborally during the operation.

The immediate effects of vagotomy were studied only in relation to gastric secretion. The interdigestive phase in esophagotomized animals was as completely abolished by bilateral vagotomy during the first twenty-four hours as by large doses of atropine (25 mg. per hundred grams or more). Acute unilateral vagotomy decreased secretion to about one third of normal. Studies on the remote effects of vagotomy were complicated by the fact that none of the vagotomized rats survived more than a week when maintained on a diet of purina checkers.® The primary cause of death in these animals was the inadequate digestion of this diet in the stomach and the failure of the stomach to evacuate its contents. Survival was significantly prolonged by the addition of choline hydrochloride to the drinking water (50 to 100 mg. a day per hundred grams of body weight). Yet the animals treated with choline remained in poor condition. Only the use of predigested proteins as a source of nitrogen helped the animals survive as long as seventeen weeks. In the bilaterally vagotomized animals the interdigestive phase of gastric secretion was greatly diminished and sham feeding failed to produce any stimulation. Thus the interdigestive phase of gastric secretion in the rat should be considered mainly a "cephalic phase."

After vagotomy, gastric motility was insufficient to evacuate solids from the stomach. Hair accumulated in tightly packed balls in the antrum at the rate of about 2 cc. every three to four weeks, so that surgical removal became necessary at these intervals. At biopsy or autopsy the esophagus was always greatly distended below the lung root, its diameter being from 5 to 10 mm., as compared with about 2 mm. in normal rats. In most cases the esophagus was filled with food and gastric contents and occasionally with masticated food masses of alkaline reaction. The cardia had the appearance of a fixed incomplete closure. The digestion and absorption of fat and the storage of glycogen by the liver were not noticeably affected by vagotomy during the four week period following the operation.

## ADDENDUM

Concurrently with our own studies, Harkins and his associates[16] were investigating the effects of vagotomy in rats. From tight ligation of the vagi below the diaphragm, these investigators reported changes in gastric secretion and in ulcer formation in rats in which the pylorus was ligated. Our results recorded in the "acute" vagotomy series are in complete agreement with these.

A summary of our preliminary results was presented in a discussion at the meeting of the American Gastroenterological Society in May 1946 and appeared in *Gastroenterology* in December 1946.[17]

16. Harkins, H. N.: The Prevention of Pyloric Ligation: Induced Ulcers of the Gastric Rumen of Rats by Transabdominal Vagotomy, Bull. Johns Hopkins Hosp. **80**:174, 1947. Harkins, H. N., and Elliott, S. R.: The Influence of Vagotomy on Ulceration of the Gastric Rumen of Rats Following Pyloric Ligation, Federation Proc. **6**:1, 1947. Harkins, H. N.; Hooker, D. H.; Alford, C., Jr.; Callander, J.; Elliott, S. R.; Kearns, W., Jr.; Mitchener, J., and Cooley, D. A.: Symposium on Vagotomy for Peptic Ulcer, Bull. Johns Hopkins Hosp. **81**:79, 1947. Harkins, H. N., and Hooker, D. H.: Vagotomy for Peptic Ulcer, Surgery **22**:239, 1947.

17. Komarov, S. A.: Discussion of Symposium on Peptic Ulcer with Particular Reference to Vagotomy, Gastroenterology **7**:620, 1946.

# FIBROSARCOMA, AN UNUSUAL COMPLICATION OF ULCERATIVE COLITIS

## Report of a Case

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THIS paper reports a rare, malignant complication of ulcerative colitis, namely, fibrosarcoma of the colon. It is becoming increasingly evident, as more statistics are published, that chronic ulcerative colitis in a significant percentage of cases may be complicated by a malignant degeneration of the colon, usually carcinomatous in type.

Lynn,[1] in an extensive review of more than 1,400 cases of ulcerative colitis, found that carcinoma developed in 1.9 per cent of the series. Jackman, Bargen and Helmholz [2] found an incidence of carcinoma of 6.3 per cent in 95 children with ulcerative colitis. Bargen, Jackman and Kerr [3] reported an incidence of 3.2 per cent in a group of 871 patients of all ages. In 450 cases of ulcerative colitis at the Lahey Clinic there was an incidence of carcinoma of 2 per cent.[4] Bockus [5] reported an incidence of about 1.5 per cent in 200 cases.

From these figures it is seen that the incidence of carcinoma of the colon in patients of all ages with chronic ulcerative colitis is 1.5 to 3.0 per cent, and this is about doubled when the studies are limited to children.

In 1928 Bargen [6] reported 20 cases of a malignant process complicating chronic ulcerative colitis. In 17 it was carcinoma, in 2 lymphosar-

1. Lynn, D. H.: The Relationship of Chronic Lesions to Carcinoma of the Colon: Chronic Ulcerative Colitis; Collective Review, Internat. Abstr. Surg. **81**:269 (Oct.) 1945.

2. Jackman, R. J.; Bargen, J. A., and Helmholz, H. F.: Life Histories of Ninety-Five Children with Chronic Ulcerative Colitis, Am. J. Dis. Child. **59**:459 (March) 1940.

3. Bargen, J. A.; Jackman, R. J., and Kerr, J. G.: Studies on Life Histories of Patients with Chronic Ulcerative Colitis, Ann. Int. Med. **12**:339 (Sept.) 1938.

4. Cattell, R. B., and Boehme, E. J.: The Importance of Malignant Degeneration as a Complication of Chronic Ulcerative Colitis, Gastroenterology **8**:695 (June) 1947.

5. Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, 1944, vol. 2, p. 593.

6. Bargen, J. A.: Chronic Ulcerative Colitis Associated with Malignant Disease, Arch. Surg. **17**:561 (Oct.) 1928.

coma and in 1 leukemia. Sarcomatous degeneration of the colon is a much more rare occurrence in cases of ulcerative colitis than is carcinoma. No other figures are available on its incidence, but only an occasional case is encountered. The usual type of sarcoma encountered is lymphosarcoma.

Fibrosarcomas of the large intestine are rare, these being more commonly found in the small intestine. They are usually firm, slowly progressive and fibrous in character. Their growth is more diffuse in character than is the typical carcinoma which tends to be rather localized. Because of this spreading type of growth, fibrosarcomas rarely cause obstruction. Late in their course they have a common tendency to bleed.

## REPORT OF A CASE

In July 1926, S. R., a married woman then 28 years of age, came under observation for ulcerative colitis. Seven years previously, at 21 years of age, she had undergone a hemorrhoidectomy, which was followed by short periods of diarrhea. This was attributed to an "ulcerated rectum" which had been caused by the operation. For one and a half years before the initial examination, the bouts of diarrhea became more frequent and lasted longer and the stools contained mucus and blood. At the time of examination she had had continuous diarrhea for three months, with a bowel movement every one or two hours accompanied with much tenesmus. She had lost 25 pounds (11.3 Kg.) in the previous year and a half and had been having "chills and fever" at night for a short time before her examination.

Examination revealed a young woman in poor general physical condition. The abdomen was "gassy" and had a poor tone. There was tenderness over the sigmoid region. The rectum revealed generalized proctitis, with superficial ulceration of the mucosa. Moderate anemia was present. Roentgenologic examination showed the stomach to be dilated, elongated and ptosed. The spleen was somewhat enlarged. The cecum was dilated and atonic. There was pronounced evidence of colitis throughout the transverse and descending colon, the sigmoid and the rectum. The colon emptied rapidly. The gastric analysis (Ewald) revealed nothing abnormal. The urine was normal except for a trace of albumin. The feces was fluid and acid. Mucus and blood were present. There was evidence of low starch digestion in the feces and a high fat loss. Culture of the feces revealed a high content of hemolytic coli and a few streptococci.

Because her improvement on medical treatment was only nominal, a cecostomy was performed in 1927 and irrigations were carried out. After this she made a distinct symptomatic improvement. She moved to Los Angeles, where she was treated by various physicians. With daily irrigations of mercurochrome® (merbromin, N. F.) solution and the use of a high protein diet, vitamins and vaccines over several years, her condition improved generally and locally (colon), although she had a recurrence of diarrhea and a reduction in health in 1929. This episode cleared under treatment by Dr. Henry Rooney, of Los Angeles. The cecostomy opening was still patent. Two years later she became pregnant, had a normal gestation and was delivered, and during her pregnancy she was surprisingly free from symptoms. She was not in New York until 1940, when she felt well. Examination revealed a rectovaginal fistula and a rectal stricture which required stretching. She was having only three or four bowel movements

a day. Because the pathologic process in the colon had advanced and because of the aforementioned stricture and fistula, an ileostomy was advised with the intention of subsequently removing the colon and rectum. Operation was refused.

The patient was not seen again until February 1946. At that time she was having considerable free bleeding from the bowel. She had lost 10 pounds (4.5 Kg.) in the preceding four months, was anemic and complained of steady pain in the sigmoid region. With difficulty, because of the rectal stricture, a large mass was felt in the left region of the pelvis and in the lower part of the abdomen. A tentative diagnosis of carcinoma was made, but a roentgenogram revealed an internal blind fistula at the center of the mass. This led to the assumption that the mass was inflammatory about the fistula. Operation was again refused, as the patient was opposed to an abdominal fecal opening.

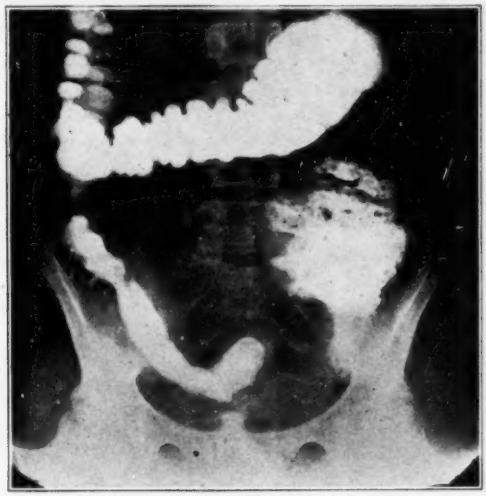

Fig. 1.—Roentgenogram showing internal fistula extending laterally from fibrosarcoma of the sigmoid.

She was not seen again until August 1947. In the interim of eighteen months she had felt somewhat stronger, but the abdominal pain and rectal bleeding had persisted. During this period an amazing episode occurred. After several days of most intense pain, she delivered through the rectum a mass of tissue "as big as her two fists." The physician called said it was some kind of a "fleshy substance, probably the tumor." There was no pathologic examination. There followed several days of alarming hemorrhage and considerable relief of pain. The patient then thought herself on the road to recovery, especially when the bleeding finally stopped.

In August 1947, when she was seen again, pain and bleeding had returned. Her general health had failed, there was severe anemia and the previously described tumor was palpable in the lower region of the abdomen. Rectal examination again

revealed the tumor, but it seemed somewhat reduced in size. Cystitis was also present. Because of the severe pain, the patient consented to operation.

At operation, performed by Dr. William Hinton, there were dense adhesions between the cecum and the lower part of the small intestine resulting from the

Fig. 2.—Photomicrograph of primary fibrosarcoma of the sigmoid; × 350.

previous cecostomy. The distal 10 inches (25.4 cm.) of ileum was definitely diseased, as was the entire colon. A mass was palpable in the lower left region of the abdomen. Ileostomy was performed, the proximal end of the ileum being brought through the lower angle of the wound and the distal end into the upper angle.

After this the pain was slightly relieved, but the bleeding continued. A month later she was reoperated on, the colon and rectum being removed. The entire colon was diseased, and the sigmoid and rectum were markedly involved by what appeared to be a granulomatous process of a stiffened type. It was adherent to the bladder and ovary, and many pelvic lymph nodes were involved. Subsequently, two masses of lymph nodes were removed from both inguinal regions.

The pathologic diagnosis was primary fibrosarcoma of the sigmoid and the upper part of the rectum, with metastatic fibrosarcoma of the ovary and the pelvic lymph nodes. The inguinal lymph nodes had undergone a similar process.

The course was steadily downhill. In about three months after operation, when considerably reduced in weight, the patient died. During the last weeks of life a hard swelling occurred in the right area of the abdomen, no doubt the result of metastasis.

## COMMENT

A case of chronic ulcerative colitis complicated by the occurrence of colonic fibrosarcoma is reported. The significance of the role played by ulcerative colitis in the production of this tumor is uncertain. Fibrosarcoma is a rare tumor of the colon, and its occurrence in the present instance may have been coincidental. On the other hand, carcinomatous degeneration of the colon in chronic ulcerative colitis is well known, and lymphosarcomas have also been reported as complications. It is evident that fibrosarcomatous degeneration of the colon is a most rare complication of chronic ulcerative colitis.

## SUMMARY

A case of chronic ulcerative colitis occurring in a woman is presented. When she was at the age of 48 years, a malignant process was first noted in the colon. At this time the duration of colitis was twenty-four years. Histologic examination revealed a primary fibrosarcoma of the sigmoid and the upper region of the rectum, with metastatic fibrosarcoma of the ovary and the pelvic and inguinal lymph nodes. The primary lesion was located in only one portion of the bowel, the rectosigmoid area.

# NEUROFIBROMATOSIS AND PSEUDARTHROSIS

## Report of a Case

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CHARLOTTE, N. C.

SINCE Barber's [1] and Ducroquet's [1b] publications in 1939, bowing of the legs, fractures and pseudarthrosis have been accepted as one of the manifestations of von Recklinghausen's neurofibromatosis. Clinically and roentgenologically the lesions are clearly described, but the morphologic changes taking place in the skeletal system are as yet not completely understood. The first, and apparently only, microscopic examination of tissue in pseudarthrosis connected with neurofibromatosis was published by Green [2] in 1943. The following report of a case of neurofibromatosis also includes the microscopic observations on tissues removed from the area of pseudarthrosis, essentially confirming those described by Green, but in addition it presents unusual features which, to our knowledge, have not been recorded in the past.

### REPORT OF A CASE

B. H., a white girl aged 3 years, 9 months, was admitted to the North Carolina Orthopedic Hospital on Jan. 28, 1947, because of nonunion of fracture of her right tibia. The past history revealed that her development had been normal. The mother noted shortly after birth that one side of the child's genitalia was larger than the other. Little attention, however, had been paid to this until the time of her fracture. The child did not menstruate or masturbate. Recently she had become conscious of herself, refusing to undress in the presence of male members of the family. There were some pigmented areas over her body, present ever since birth. These had not increased in number. No nodules or growth had been noticed on her body. Her appetite had been poor, diet consisting mainly of crackers and soft drinks.

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From the Charlotte Memorial Hospital, Charlotte, N. C., and the North Carolina Orthopedic Hospital, Gastonia, N. C.

Dr. Thompson holds the title of Orthopaedic Fellow, The National Foundation for Infantile Paralysis, Incorporated, New York.

1. (*a*) Barber, C. G.: Congenital Bowing and Pseudarthrosis of the Lower Leg: Manifestations of von Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **69**:618-626, 1939. (*b*) Ducroquet, cited by Barber.[1a]

2. Green, W. T., and Rudo, N.: Pseudarthrosis and Neurofibromatosis, Arch. Surg. **46**:639-651 (May) 1943.

Fig. 1.—Clitoris.

Fig. 2.—Pseudarthrosis of tibia and fibula. The bowing of the tibia and erosion of the cortex in its upper one third are readily visible. Also seen is an intracortical cyst in the posterior aspect close to and above the fracture of the tibia.

The family history revealed the mother to be 23 years of age, with many pigmented areas on her body for as long as she could remember. The menarche had occurred at the age of 15, and her menstrual history was normal. The father, aged 27 years, had no fractures and no pigmentation or nodular growths on the body. Her maternal grandmother, aged 43, had numerous small nodular growths on the upper part of the chest, neck, face and back. These had been present since the age of 16. Her menstrual history was normal. The maternal grandfather, aged 68, had small nodular growths localized on the trunk. The maternal first cousin sustained a fracture of her tibia at the age of 10. No union occurred. She is now 16 years of age and is unable to walk without the aid of a brace. The patient had no brothers or sisters.

Fig. 3.—Section through the tissue between fracture ends showing streaming of nuclei, palisading and fascicular arrangement.

*Present History.*—The patient fell down four steps, sustaining a fracture of the left tibia, in September 1946. The treatment consisted of reduction of the fracture and application of a plaster cast by an orthopedist. Roentgenologic examination six weeks later failed to reveal any evidence of callus formation. Ten weeks after fracture, the cast was removed, and roentgenologic examination at that time revealed lack of callus formation, with some absorption of bone at the fracture site and spike formation at the distal end of the proximal fragment.

At the time of the patient's admission to the hospital, fifteen weeks after injury, examination revealed a fairly well developed and well nourished blond

girl. She presented café au lait spots on the right side of her thorax and abdomen, their long dimensions running transverse to the body axis. Her clitoris (fig. 1) was greatly enlarged, measuring 4 by 2 cm. There was no pubic hair, and her breasts were infantile. The vagina and the external genitalia were otherwise normal. The left tibia exhibited clinically an ununited fracture in the lower third, with a typical pseudarthrosis (fig. 2).

*Laboratory Findings.*—The Wassermann test gave a negative reaction. A stool specimen was normal, and a vaginal smear was sterile. The urine was normal. The hemoglobin content was 82 per cent, the red blood cells numbered 4,430,000, and white blood cells 7,250, the calcium content was 11.1 mg. per hundred cubic centimeters, the phosphorous 4.7 mg. and alkaline phosphatase 3.7 Bodansky units.

*Course in the Hospital.*—A biopsy was performed on Feb. 24, 1947, and after this a double cortical onlay graft was performed, the right tibia being used as a donor site.

The microscopic examination showed portions of the fractured ends of well formed lamellar bone in continuity with a large mass of connective tissue. The latter enclosed small fragments of necrotic bony spicules and a small area of new formation of bone by direct metaplasia. The main portion of connective tissue was made up of spindle-shaped elements arranged in a parallel and occasionally fascicular fashion, which revealed whorl formation in many areas and at one point distinct palisading of nuclei (fig. 3).

At the time of writing it is only two months since operation, and the final result is undetermined.

## COMMENT

*A. Changes in Bony Structures and Pseudarthrosis.*—Two, perhaps independent, structural changes were present in the tibia prior to the fracture: first, a cortical erosion with underlying zone of hyperostosis; and, second, an "osteomalacic" process involving the entire tibia, resulting in bowing. The superficial erosion may have been caused by periosteal neurofibromas or by true intraosseous neurofibroma as described by Friedman [3] and others. The "osteomalacic" process, to which many authors refer, would explain the bowing of the long bone and the deformities in other portions of the skeleton but has actually not been demonstrated. Green [2] merely found enlargement of the haversian canals in material from an area of cortical thickening. Brooks and Lehman [4] spoke of increased osteoporosity, but true osteomalacia characterized by destruction of calcified bone and slow replacement by uncalcified osteoid tissue has not been described (Weinmann

3. Friedman, M.: Neurofibromatosis of Bone, Am. J. Roentgenol. **51**:623-630, 1944.

4. Brooks, B., and Lehman, E. P.: The Bone Changes in von Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **37**:587-592, 1924.

and Sicher).[5] The deformities and segmental abnormal growth have hypothetically been ascribed to hyperplastic changes in the lymphatic vessels or to neurinomatous growth in the epiphyseal line (Brooks and Lehman).[4] Moore [6] postulated lack of growth control from neurinomatous changes in the supplying nerve. This assumption is supproted by roentgenographic and histologic observations. In a case of neurofibromatosis with localized overgrowth, Moore [6] has clearly demonstrated the absence of horizontal lines of cessation of growth. Although uncontrolled growth may account for the deformities, it does not explain the mechanism of fracture, which in most instances is more or less spontaneous. Kite,[7] explaining the mechanism of fracture, assumed that atrophy and cyst formation cause softening and diminution of the diameter of the shaft, thus allowing the tibia to bend. It is, however, not certain that atrophy actually occurs. The bony architecture may appear rarefied because of defective growth rather than regression. Furthermore, atrophy as well as cyst formation will render the bone frangible rather than flexible. Actual destruction of bone by subperiosteal or intraosseous neurofibromas with so-called subperiosteal cysts must be assumed as the cause of fracture, but further confirmation of this only scantily substantiated hypothesis is needed.

After a fracture has taken place, there is a lack of proper callus formation. Moore [6] assumed that this is likewise due to improper control of bony growth. Since then, however, the actual appearance of neurofibromatous tissue between the fracture ends and the occurrence of intraosseous neurofibroma have been demonstrated (Green [2] and Friedman [3]). Our case may be added to this list. We agree with Green that it is often difficult to distinguish histologically between neurofibroma and nonspecific connective tissue unless nerve fibers can be demonstrated (McNairy and Montgomery [8] and Schlumberger [9]). We have recognized the tissue within the area of pseudarthrosis in our case as neurofibromatous purely on the basis of its dis-

5. Weinmann, J. P., and Sicher, H.: Bone and Bones, St. Louis, C. V. Mosby Company, 1947.

6. Moore, B. H.: Some Orthopaedic Relationships of Neurofibromatosis, J. Bone & Joint Surg. **23**:109-140, 1941.

7. Kite, J. H.: Congenital Pseudarthrosis of Tibia and Fibula, South. M. J. **34**:1021-1032, 1941.

8. McNairy, J. D., and Montgomery, H.: Cutaneous Tumors of von Recklinghausen's Disease (Neurofibromatosis): Report of Histologic Study, with Special Reference to Nerve Fibers and the Bodian Stain, Arch. Dermat. & Syph. **51**:384-390 (June) 1945.

9. Schlumberger, H. G.: Fibrous Dysplasia of Single Bones: Monostotic Fibrous Dysplasia, Mil. Surgeon **99**:504-527, 1946.

tinct histologic pattern and because a neurofibromatous nerve was found in the periosteal tissue. Zenker's fixation prohibited silver stain for nerve fibers.[10]

As pointed out by Jaffe,[11] we cannot agree with Thannhauser [12] that whorl formation by itself is pathognomonic of neurofibroma. The palisade arrangement of nuclei, the fascicular arrangement of fibers, the uniformity of the tissue and its connection with a neurinomatous nerve assured us of its neurogenic origin. The correctness of our diagnosis was subsequently verified only by the investigation of other members of the family.

The finding of bone formations, observed in our case, by direct metaplasia from the tumor tissue proper requires consideration. We hold with Jaffe [11] that neurofibroma, in contrast to fibrous dysplasia, does not form bone. It must, therefore, be assumed that the bone spicula was formed in an area where endosteum or periosteum imperceptibly blended into neurofibromatous tissue.

A critical and objective analysis of the histologic interpretation is not only of academic interest. If the pseudarthrosis is purely of connective tissue origin, it would bear out Moore's [6] contention that disturbance of growth is the primary factor. If ingrowth of neurofibroma prevents union, we are dealing with a tumor formation, and treatment should be directed accordingly.

*B. Constitutional Changes.*—A great number of lesions have been added to von Recklinghausen's original one of neurofibromatosis as part and parcel of this disorder. Among these we shall refer only to the endocrine changes and the pigmentation of the skin. Our patient showed a greatly enlarged clitoris and café au lait spots entirely within the level of the skin. Hypertrophy of the clitoris, to our knowl-

10. After completion of this paper we have had the opportunity of studying tissue removed from the site of the pseudarthrosis in 2 cases of neurofibromatosis with congenital pseudarthrosis. In neither of these was there a histologic pattern as distinctly indicative of neurinomatous growth as that observed in the original case. Massive new growth of young connective tissue in a streaming fascicular fashion was observed, but palisading of nuclei could not be demonstrated. Although not pathognomonic, the histologic observations are compatible with neurofibromatous growth. (The histologic study of the biopsy specimen in these cases was made possible through the courtesy of Dr. Warren White, Greenville, S. C., and Dr. J. H. Kite, Atlanta, Ga.)

11. Jaffe, H. L.: Fibrous Dysplasia of Bone: A Disease Entity and Specifically Not an Expression of Neurofibromatosis, J. Mt. Sinai Hosp. **12**:364-381, 1945.

12. Thannhauser, S. J.: Neurofibromatosis (von Recklinghausen) and Osteitis Fibrosa Cystica Localisata et Disseminata (von Recklinghausen): A Study of a Common Pathogenesis of Both Diseases, Differentiation Between Hyperparathyroidism with Generalized Decalcification and Fibrocystic Changes of the Skeleton and Osteitis Fibrosa Cystica Disseminata, Medicine **23**:105-149, 1944.

edge, has hitherto been mentioned only twice in connection with neurofibromatosis. In fact, this phenomenon stands in contrast to most previously described manifestations of inner secretory disturbances. Most authors attempt to explain these by pressure of neurofibromas on the glands of inner secretion and the various types of disturbances, resulting mostly in retarded sexual development (Uhlmann and Grossman).[13] Others assume that endarteritis causes changes in the function of glands of inner secretion (Moore[6]). Thannhauser[12] has collected 4 cases from the literature in which there was evidence of precocious puberty and added a fifth case of his own. The classification of this last case, however, as one of neurofibromatosis has not been accepted generally (Jaffe[11]).

Whether the enlargement of the clitoris in our case can be regarded as manifestation of precocious puberty remains questionable. There is the possibility of unrecognized hermaphroditism and that of neurofibromatous change in the clitoris. The latter, however, is not likely, since no cutaneous nodes were demonstrable. On the other hand, the child showed no signs of prematurity. The breasts were those of a child of her age. She did not menstruate, and there was no history of masturbation. The bone age was also in keeping with her stated age. We are thus inclined to register the hypertrophy of the clitoris as another manifestation of neurofibromatosis, perhaps "overgrowth," and not necessarily of sexual precocity.

The café au lait spots cannot be regarded as an absolute criterion of neurofibromatosis if they show no elevation due to beginning changes in the corium. It is the family history in this case that proved the foci of pigmentation to be a manifestation of von Recklinghausen's neurofibromatosis.

*C. Neurofibromatosis Versus Fibrous Dysplasia.*—Thannhauser,[12] on the basis of a detailed analysis of the literature, suggested that neurofibromatosis and fibrous dysplasia (osteitis fibrosa cystica disseminata) are related disorders. He attempted to prove this contention by a collection of case reports from the literature in which both conditions in the same patient were described. The actual morphologic changes underlying the poorly described roentgenologic findings in the skeleton, however, are not mentioned. He stated that café au lait spots are as pathognomonic of neurofibromatosis as the cutaneous nodule itself, although the histologic changes in the skin, as pointed out by Jaffe,[11] are different in the two conditions. He also regarded the whorl formation in fibrous dysplasia as additional evidence of neurofibromatosis. Thannhauser's[12] concept was sharply denounced by Jaffe,[11] and it

13. Uhlmann, E., and Grossman, A.: Von Recklinghausen's Neurofibromatosis with Bone Manifestations, Ann. Int. Med. **41**:225-241, 1940.

has to be admitted that Jaffe's [11] statements seem to bear out his contention that the two disorders are unrelated. The most important points of difference relate to the pattern of osseous lesion and to the hereditary factor. In fibrous dysplasia the lesion occurs primarily within the bone, with new formation of bone spicules. In neurofibromatosis the lesion is situated mostly at the surface, eroding the latter, is rarely within the shaft and never shows new formation of bone. In fibrous dysplasia no familial occurrence is known, while neurofibromatosis is predominantly familial. On the basis of our previous experience with both conditions, Jaffe's [11] depicture must be accepted as clear evidence of the different appearance in the two. The differences outweigh certain resemblances.

The constitutional manifestations in the case we presented were suggestive of osteitis fibrosa cystica. Cutaneous nodules were absent, but café au lait spots and an enlarged clitoris were demonstrated, a combination rarely seen in neurofibromatosis. On the other hand, the family history and the nature of bony changes left no doubt about the true neurofibromatous character of the condition.

The cause of neurofibromatosis or of generalized fibrous dysplasia is not known. Hence, if there are features of resemblance or if cases are reported which present manifestations common to both conditions, it cannot be flatly denied that the entity of generalized fibrous dysplasia may not constitute a subgroup of a general disorder which includes neurofibromatosis. It is true that no hereditary factor has been demonstrated in the relatively small series of cases of generalized fibrous dysplasia, but, conversely, in only 43 per cent of the cases of neurofibromatosis can hereditary tendencies be proved (Uhlmann and Grossman [13]).

The case we presented does not support Thannhauser's [12] concept of the correlation of the two conditions. In spite of certain peculiar aspects, it must be classified as a case of neurofibromatosis. It does, however, demonstrate the confusing character of the so-called constitutional signs and the need for more extensive morphologic examination of the underlying bony lesion.

## SUMMARY

A case of so-called congenital pseudarthrosis of the tibial bone is presented.

The patient was a member of a family with hereditary von Recklinghausen's neurofibromatosis, and these findings of significance were noted: (*a*) presence of neurofibromatous tissue between the ends of the fractured bone and (*b*) constitutional signs, simulating those of osteitis fibrosa cystica, namely café au lait spots and enlarged clitoris.

# EXPERIMENTAL INJURY OF THE COMMON BILE DUCT

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IT IS DIFFICULT or impossible to determine the incidence of injuries of the hepatic or common bile ducts which occur in the course of operations on the biliary system. Kehr [1] in 1913 reported injury to the common and hepatic ducts fifteen times in one thousand cholecystectomies, or an incidence of 1.5 per cent. Jacobson [2] reviewed the literature up to 1914 and found only 34 cases. Since then, other injuries of this type have been described (Eliot [3] and Eisendrath [4]), but the reviews do not give an accurate idea of the frequency of injury of the common duct since most cases are not reported.

Injuries to the common duct may occur as a result of inflammation of the duct or trauma to the duct. Cole and his associates [5] reported that 76 per cent of a series of strictures were the result of operative injury, Cattell [6] 80 per cent and Walters [7] 90 per cent. In contrast to these, Judd [8] felt that many of the cases attributed to operative trauma were in reality due to ascending cholangitis. As he pointed out, trauma is blamed for many strictures even though the operation thought to be at fault occurred months before. However, not enough is known about the cause of this type of cholangitis for one to duplicate

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1. Kehr, H.: Die Praxis der Gallenwege-Chirurgie, München, J. T. Lehmann, 1913, vol. 1, p. 183.

2. Jacobson, J. H.: Repair and Reconstruction of the Bile Ducts, Am. J. Obst. **70**:948-965, 1914.

3. Eliot, E.: The Repair and Reconstruction of the Hepatic and Common Bile Ducts, Surg., Gynec. & Obst. **26**:81-102, 1918.

4. Eisendrath, D. N.: Operative Injury of the Common and Hepatic Bile Ducts, Surg., Gynec. & Obst. **31**:1-18, 1920.

5. Cole, W. H.; Ireneus, C., Jr., and Reynolds, J. T.: The Use of Vitallium Tubes in Strictures and Absence of the Common Bile Duct, Ann. Surg. **122**:490-521, 1945.

6. Cattell, R. B.: Benign Strictures of the Bile Ducts: Causes and Methods of Repair, S. Clin. North America **23**:701-713, 1943.

7. Walters, W.: Strictures and Injuries of Bile Ducts: A Study of Results of Operations in Eighty Cases, J. A. M. A. **113**:209-213 (July 15) 1939.

8. Judd, E. S.: Stricture of the Common Bile Duct, Ann. Surg. **84**:404-410, 1926.

it experimentally, and this paper is concerned only with lesions of the common duct produced by direct trauma.

Traumatic lesions of the common duct may be produced in various ways: 1. The duct may be accidentally crushed during an operation. 2. A ligature may be applied to the duct. 3. The duct may be partially or completely cut. 4. A portion of the duct may be accidentally excised. 5. The duct may be cut longitudinally (this is, of course, intentionally done in choledochotomy). 6. The mucous membrane of the duct may be injured by too vigorous probing and scooping. 7. A stone, by long residence in the common duct, may produce injury of the wall of the duct, and it is possible that the passage of a large stone may be followed by mucosal damage.

Eisendrath [4] reviewed the series of Jacobson [2] and that of Eliot [3] in 1920 and also the literature from that date, and he found only 51 cases of injury of the bile ducts due to anatomic variations or errors in technic. The other cases in the literature examined by him involved injuries incident to factors other than errors in technic or anomalies, such as the pathologic changes due to biliary infection.

Since injuries of the duct produced in known ways are not often encountered in man at an optimum time to determine the exact effect of the lesions, the experimental approach has a definite advantage.

## EXPERIMENTAL PROCEDURE

1. *Operative Technic.*—All operations were performed on dogs under strict surgical asepsis. The abdomen was entered through an incision in the upper midline or right paramedian areas. The lesser curvature of the stomach and the first part of the duodenum were pulled caudad to bring the hepaticoduodenal ligament into view. The external biliary system was then identified and the various procedures carried out. Cotton was ordinarily used for wound closure and silk rarely used.

2. *Anesthesia.*—Morphine and ether intratracheally or a combination of morphine sulfate and pentobarbital was used in all cases. For the morphine-pentobarbital (pentobarbital sodium U. S. P.) anesthesia, 3 mg. of morphine sulfate per kilogram of body weight was given intraperitoneally in 10 cc. of distilled water at least thirty minutes, but preferably sixty minutes, before 50 mg. of pentobarbital per kilogram of body weight was given intraperitoneally or intravenously in 10 cc. of distilled water. Intravenously the barbiturate acted almost immediately and intraperitoneally about five minutes after injection. In rare instances it was necessary to supplement the morphine-pentobarbital anesthesia with up to an additional 20 mg. per kilogram of pentobarbital in distilled water intravenously.

3. *Icterus Index.*—Patency of the bile duct was determined by the presence of excessive bilirubin in the bloodstream. A standard solu-

tion of potassium dichromate was prepared and placed in test tubes in various dilutions.[9] The tubes were sealed, and thus permanent standards, representing 0 to 100 units, were obtained for comparison with unknown serum samples. The colorimetric determinations were done grossly and not in a colorimeter since we were interested only in large increases in the blood bilirubin level.

Because of hemolysis, the icterus index was determined by the method advocated by Harrison.[10] After a clot was allowed to form in the refrigerator overnight, the sample was centrifuged and the serum removed. To 2 cc. of serum an equal amount of acetone was added to precipitate serum albumin and globulin. After spinning down, the supernatant protein-free layer was removed and compared with the color standards and the value obtained multiplied by 2. Of course, some bile is precipitated along with the hemoglobin, but the amount is negligible. The normal by this method is 0 to 8 units.

### LIGATION OF THE COMMON BILE DUCT

This type of trauma appears often in classifications of causes of stricture of the bile ducts, but as far as reported cases[11] are con-

9. Kolmer, J. A., and Boerner, F.: Approved Laboratory Technic, ed. 4, New York, D. Appleton-Century Company, Inc., 1945, p. 228.

10. Harrison, G. A.: Chemical Methods in Clinical Methods, London, J. & A. Churchill, Ltd., 1943, p. 261.

11. (*a*) Aynesworth, K. H.: Stricture of the Common Bile Duct, Am. J. Surg. **28**:562-568, 1935. (*b*) Behrend, M.: Obliteration of the Common Bile-Duct Following Operation: Cured by an Hepaticoduodenostomy, Ann. Surg. **68**:32-33, 1918. (*c*) Bettman, R. B., and Tannenbaum, W. J.: Complication Arising from Use of Vitallium Tube for Common Duct Repair, J. A. M. A. **129**:1165-1166 (Dec. 22) 1945. (*d*) Colp, R.: Hepatico-Duodenal Intubation with Hepato-Duodenostomy for Traumatic Stricture of the Hepatic Duct. Surg., Gynec. & Obst. **80**:190-196, 1945. (*e*) Douglas, J. D.: Strictures and Operative Injuries of the Bile Ducts, Ann. Surg. **84**:392-403, 1926. (*f*) Erdmann, J. F.: Reconstruction of the Bile-Ducts, Ann. Surg. **67**:370-371, 1918. (*g*) Fowler, W. F.: Reconstruction and Repair of the Hepatic and Common Bile-ducts, Surg., Gynec. & Obst. **27**:387-392, 1918. (*h*) Horsley, J. S., and Horsley, G. W.: Cholecysto-Enterostomy, Choledocho-Enterostomy and Entero-Enterostomy by Means of Rubber Bands: The Use of Rubber Bands in the Mikulicz Operation, Ann. Surg. **118**:558-575, 1943. (*i*) Judd, E. S., and Parker, B. R.: Mortality Following Operations on the Biliary Tract, Pancreas and Liver, Ann. Surg. **84**:419-437, 1926. (*j*) Lilienthal, H.: Injury to the Common Duct, Ann. Surg. **67**:619-621, 1918. (*k*) Mayo, W. J.: Some Remarks on Cases Involving Operative Loss of Continuity of the Common Bile Duct, Ann. Surg. **42**:90-96, 1905. (*l*) McCurrich, H. J.: A New Operation for Restoration of the Common Bile Duct Following Accidental Damage, Brit. J. Surg. **31**:304-305, 1944. (*m*) Migliaccio, A. V.: Reconstruction of Common Duct with Vitallium Tubes, Am. J. Surg. **70**:261-267, 1945. (*n*) Pearse, H. E.: Benign Strictures of the Bile Ducts Treated with a Vitallium Tube, Surgery **10**:37-44, 1941. Cole, Ireneus and Reynolds.[5] Eisendrath.[4] Eliot.[3] Jacobson.[2] Kehr.[1]

cerned, actual simple encirclement of the common bile or common hepatic duct with a ligature and the duct left uncut is not common (see table). In the other cases having to do with ligation, only part of the wall of the duct was included in the ligature or a knuckle of the duct was tied as observed by Phemister [12] or the duct was clamped, ligated and cut. In the last case, obstructive symptoms and signs develop while the ligature holds, and when it gives way, external biliary fistula occurs. Allen [13] has removed chromic surgical gut ligatures from the end of a common duct severed at operation a month earlier. In accidents such as the one just described, ligation is of secondary importance in production of the injury since the main source of trauma

*Reported Cases of Simple Ligation of Common Duct*

| | | | |
|---|---|---|---|
| Lilienthal, H. | Cholecystectomy | Hepatic duct mistaken for cystic duct and ligated | Found at necropsy |
| Bottomley, J. T. | Cholecystectomy | Common hepatic duct almost completely occluded by ligature about cystic duct and artery | Ligature removed at secondary operation and patient recovered |
| Phemister, D. B. | Cholecystectomy | Knuckle of hepatic duct included in ligature controlling cystic artery hemorrhage | Fistula formed |
| Eisendrath, D. N. | Cholecystectomy | Part of hepatic duct ligated controlling cystic artery hemorrhage | No stricture |
| Russell, T. H. | Cholecystectomy | Complete ligation of common duct | Ligature removed at secondary operation; T tube which was inserted pulled out and was followed by stricture |
| Brewer, G. E. (personal communication to Eliot [2]) | Cholecystectomy | Partial ligation of the common hepatic duct | Healed without occlusion |
| Russo, C. | Cholecystectomy | Mass litigation of the common duct | Found at necropsy |
| Douglas, J. | Cholecystectomy | Clamp and suture ligature to control bleeding | Fistula formed |

is the improper application of forceps, resulting in cutting or resection of the duct. From the tabulation it is apparent that when a portion of the duct was ligated the wall under the ligature was deprived of its blood supply and sloughed, allowing bile to pour into the abdominal cavity, or, contrastingly, healed without occluding the ductal lumen. Of the 3 cases in which a loop of ligature was placed around the duct and the duct left intact, 1 was found at autopsy [14] and the other 2 at secondary

12. Phemister, D. B.: Reconstruction of the Hepatic Duct, Surg. Clinics, Chicago **1**:553-560, 1917.

13. Allen, A. W.: A Method of Re-Establishing Continuity Between the Bile Ducts and the Gastro-Intestinal Tract, Ann. Surg. **121**:412-424, 1945.

14. Russo, C.: Five Years of Gall Bladder Surgery in a General Hospital: A Review of Three Hundred and Thirty-Seven Consecutive Gall Bladder Operations. Am. J. Surg. **58**:388-397, 1942.

operation for biliary obstruction. Bottomley's patient [15] recovered when the ligature was cut at reoperation. Russell [16] cut the ligature but also did a choledochotomy with a T tube drainage at secondary operation. The tube was removed, and a month later he reoperated for obstruction and found a stenosis of the duct 1 inch (2.5 cm.) long at the site of choledochostomy. The literature reviewed did not contain a report of a case in which the duct was ligated, the ligature cut at a second operation and stricture formed.

In studies on the effect of operations on the gallbladder, McWhorter [17] ligated the cystic duct of 7 dogs with plain fine surgical gut, and the latter was absorbed in ten to fourteen days without stricture or scarring of the duct over a period of one week to four months. In 5 animals the cystic duct, ligated with surgical gut, failed to reopen. Two of these ducts reopened after only seven postoperative days, but the other three were found occluded at the end of one to five months. According to this observer, the duct becomes patent unless unnecessary trauma or heavy suture material is used, and he suggested that "temporary ligation of the bile ducts with fine catgut may aid in controlling hemorrhage, especially about the cystic duct, and in the diversion of bile."

*Experimental Data.*—The common bile ducts of 10 dogs were ligated and the ligatures left in place for varying periods to observe the effect of this type of trauma on the bile ducts. The ducts of 8 of these animals were tied with cotton. This nonabsorbable ligature was removed successfully, unsuccessfully or not at all, as the case may be, in a given period. In 2 dogs the duct was tied with different sizes of plain surgical gut and left permanently.

CONDENSED PROTOCOLS

1. In dog 23 the common bile duct was tied with white cotton on April 1, 1947. The icterus index was 12 units on the second postoperative day, 16 units on the third day and 30 units on the fourth day. On April 10 an attempt was made to remove the ligature from the duct, but the wall of the duct gave way and the animal died.

2. In dog 47 the common duct was ligated with cotton on March 8, 1947. The icterus index was 100 units on March 10, and the ligature was successfully removed. The dog recovered and no pathologic change was seen in the duct at necropsy on July 15, 1947.

3. In dog 49 the common bile duct was ligated with black cotton on Oct. 10, 1946. The icterus index rose to 50 units on October 13 and 100 units on October 16, remained elevated for a time and returned to normal. Necropsy on December 14

15. Bottomley, J. T.: Personal communication to Eisendrath.[4]

16. Russell, T. H.: Reconstruction of Common Bile Duct: Seven Year Result, Ann. Surg. **111**:145-147, 1940.

17. McWhorter, G. L.: Clinical and Experimental Operations on the Gallbladder and Common Duct: Results of Primary Suture, Arch. Surg. **35**:1099-1125 (Dec.) 1937.

showed dilated gallbladder and ducts down to the ligature, normal below this, and bile in the duodenum.

4. In dog 51 the common duct was ligated with white cotton on Oct. 10, 1946. Two days later the icterus index was 100 units, and it remained elevated until October 27, when it was found normal. The icterus index was repeatedly normal after this. At reoperation on December 12 the common duct was found to be patent though larger than normal, and no ligature could be seen.

5. In dog 81 the common bile duct was ligated with cotton on March 18, 1947. On March 20 the icterus index was 20 units and the ligature was removed. The gallbladder and duct were dilated and the animal made an uneventful recovery. Necropsy was performed on April 21, 1947. Bile was found in the duodenum and the common bile duct was patent though slightly dilated above the site of the old ligature.

6. In dog 82 cholecystectomy was performed; the common bile duct was ligated twice with cotton on Jan. 17, 1947. On Jan. 21 the icterus index was 100 units, and it remained elevated. At reoperation on January 24 to remove the ligature the wall of the tremendously dilated proximal duct was nicked accidentally and the dog died.

7. In dog 97 the common duct was ligated with cotton on March 20, 1947. On March 22 the icterus index was 8 units and the ligature was removed. The gallbladder was six times the normal size and the common duct the size of a lead pencil. The dog recovered. At necropsy on April 23 the duct appeared normal.

8. In dog 110 the common bile duct was ligated with no. VIII cotton on April 3, 1947. The icterus index was 6 units on April 5, 12 units on April 6 and 40 units on April 10, and it remained elevated. On May 17 the duct perforated during an attempt to remove the ligature, but the animal recovered. Necropsy was performed on July 10. The common duct was intact and patent.

9. In dog 187 the common bile duct was ligated with no. II plain surgical gut on June 7, 1947. On June 12 the icterus index was 14 units, on June 18, 27 units and on June 25, 0 units. At necropsy on July 18 the common duct was larger than usual but patent.

10. In dog 188 the common bile duct was ligated with no. III plain surgical gut on June 14, 1947. The icterus index was 20 units on June 18, 4 units on June 25 and 6 units on June 27. At necropsy the common duct was enlarged but stricture was not apparent. There was bile in the duodenum.

*Summary and Conclusions.*—1. Heavy plain surgical gut placed about the common ducts of 2 dogs was absorbed, and the biliary obstruction was relieved. 2. A nonabsorbable ligature on the common duct can be removed after several days, and the animal will recover. Stricture did not develop subsequently during the period of observation. In dog 41 the ligature was definitely in place ten days before slipping without producing a stricture. In another animal, dog 49, the duct was patent proximal and distal to the ligature, which had slipped a little, allowing bile to pass into the duodenum sixty-nine days after operation. 3. When trying to remove a ligature from the duct at secondary operation, care must be exercised to avoid pulling the ligature too hard. 4. Among 2 dogs injured in this way, healing occurred in 1, dog 110, and that without stricture.

### CRUSHING OF THE DUCT

This is another type of trauma frequently noted in classifications of injury of the bile duct. Surprisingly, there are few case reports in the literature from which one could assume that the actual trauma of clamping has been responsible for injury to one of the bile ducts. Pearse [11n] reported a case in which the upper part of the common duct was clamped while controlling hemorrhage from the cystic artery and the clamp left on. It is questionable whether the ultimate stricture was due to this or to choledochotomy performed at secondary operation. When the majority of case reports speak of "clamping of the duct," the act of clamping is followed usually by ligation and cutting or by ligation alone of a portion of the duct.

*Experimental Data.*—The common ducts of 5 dogs were crushed for varying lengths of time with large Ochsner forceps.

#### CONDENSED PROTOCOLS

1. In dog 10 the common duct was crushed for ten minutes with large Ochsner forceps on Nov. 14, 1946. Recovery up to November 22 was uneventful. On this date evisceration occurred, and reclosure was attempted but the dog died. At necropsy the common duct appeared thicker than normal and slightly dilated. There was no sign of obstruction.

2. In dog 30 the common bile duct was clamped with Ochsner forceps for five minutes on Feb. 27, 1947. The icterus index remained normal, and necropsy, on July 2, 1947, revealed a normal duct.

3. In dog 85 the common duct was crushed for ten minutes with large Ochsner forceps on March 11, 1947. Recovery was uneventful. The icterus index was repeatedly normal until death occurred on April 27 from distemper. At necropsy the gallbladder was three times normal size and the common duct a little larger than normal.

4. In dog 48 the duct was crushed for ten minutes on March 11, 1947, with a large Ochsner forceps. The icterus index remained normal, and the animal was killed on April 30. At necropsy the gallbladder was normal. The common bile duct was possibly a little dilated.

5. In dog 11 the common duct was crushed for ten minutes on Nov. 14, 1946. There was a normal icterus index, but the animal died on November 22 of distemper.

*Summary and Conclusions.*—No jaundice was noted in 5 dogs after the ducts were crushed for ten minutes with an Ochsner forceps, but in about half the animals there was dilatation of the ducts.

### CUTTING OF THE DUCT

Statements regarding the regenerative properties of the bile ducts have appeared from time to time. Sullivan [18] stated that he cut the common duct in the hepaticoduodenal ligament experimentally and that

18. Sullivan, A. G.: Reconstruction of Bile Ducts, J. A. M. A. **53**:774-777 (Sept. 4) 1909.

invariably it healed without anything further being done. Others have commented on the remarkable regenerative powers of the duct,[19] and ducts reconstructed experimentally [20] and clinically [21] eventually became lined by the epithelium of the bile duct mucosa.

Cutting is frequently a cause of injury to the bile passages. Fortunately, injuries to the duct in this manner are fairly often recognized at primary operation and the damage repaired at that time. Stricture has been reported after such repairs.

*Experimental Data.*—To observe this phenomenon, the common ducts of several dogs were simply severed, or a section was removed, or the duct was hemisectioned or a section was removed and the cut ends anastomosed.

CONDENSED PROTOCOLS

1. In dog 30 a 2 cm. portion of the common duct was removed and the cut ends left free in the hepaticoduodenal ligament on Oct. 22, 1946. There was a gradual rise in the icterus index to 100 units on November 4. At necropsy the cut ends of the duct were isolated by a mass of fibrous tissue. There were no signs of anastomosis or regeneration.

2. In dog 142 removal of 1 cm. of the common duct and anastomosis of the cut ends with fine silk were accomplished on April 9, 1947. Recovery up to April 20 was uneventful and then jaundice developed, and the animal was found dead on April 27. At necropsy leakage at the site of anastomosis was seen.

3. In dog 72 the duct was cut in the hepaticoduodenal ligament on Feb. 27, 1947. The icterus index was 100 units on March 4, 1947. The dog was found dead on March 7. At necropsy there was bile in the peritoneal cavity. No anastomosis was seen.

4. In dog 42 the common duct was cut in the hepaticoduodenal ligament on Jan. 10, 1947. The icterus index was 0 units on January 10 and 18. On January 21 it was 21 units, and on January 30 it was 30 units. Deepening jaundice appeared, and the dog died on March 4. At necropsy the gallbladder and biliary tree were enormously dilated. The distal portion of the common duct was found to end near the greatly dilated portion of the proximal segment of the common duct, but no continuity could be demonstrated between the two.

5. In dog 150 the common duct was cut in the hepaticoduodenal ligament on March 8, 1947. On March 10 the icterus index was 20 units, and it increased thereafter to 100 plus. Jaundice became intense. The dog died on April 2. At necropsy there was bile in the peritoneal cavity. The cut ends of the common duct were separated 1.5 cm. The distal duct was normal in appearance. The proximal duct was dilated three times normal. There was no anastomosis.

6. In dog 160 the common duct was cut half-way through with scissors on March 15, 1947. The icterus index remained normal. The dog was killed on June 6. At necropsy the common bile duct appeared normal.

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19. Eliot, E.: Benign Cicatricial Strictures of the Bile Ducts, Ann. Surg. **104**:668-701, 1936. Jacobson.[2]

20. Danis, R., cited by Jacobson.[2] Sullivan.[18]

21. Jenckel, cited by Jacobson.[2] Roeder, C. A.: Transplantation of a Biliary Fistulous Tract Into the Duodenum, Ann. Surg. **91**:144-147, 1930.

7. In dog 111 the common duct was hemisectioned on March 15, 1947. There was no rise in the icterus index. The dog was killed on April 16. At necropsy the duct appeared normal.

*Summary and Conclusions.*—1. The severed common bile ducts of 3 dogs failed to anastomose or regenerate after nine, twenty-six and fifty-four days respectively. 2. A 2 cm. section of common duct was removed from 1 dog, but no anastomosis occurred in forty-six days. 3. A 1 cm. piece of common duct was removed from another dog and the ends anastomosed, and partial union occurred in eighteen days. 4. The common duct was hemisectioned in 2 dogs and healed perfectly without obstruction. 5. In view of these observations on healing together with those noted after choledochotomy (ulceration of the duct) and severance of the duct while removing a ligature, it would seem that healing of the common duct, in the dog at least, is not as remarkable as is perhaps generally believed and that healing is best promoted, as elsewhere, by contiguity of cut surfaces.

## ULCERATION OF THE COMMON BILE DUCT

A method could not be devised which would include all the factors present during ulceration of the duct by an impacted stone. A procedure was employed, however, which destroyed the mucosa and perhaps some of the underlying layers, to reproduce the actual destruction of the mucosa by stone and to equal, in intensity at least, the trauma produced by too violent scooping or probing of the duct during choledochotomy.

*Experimental Data.*—Choledochotomy was performed on 2 dogs. The wall of the common duct was cauterized by a crystal of phenol and the effect neutralized with alcohol when whiteness persisted for at least thirty seconds and left open.

### CONDENSED PROTOCOLS

1. In dog 143 the common bile duct was opened and a phenol crystal touched to the wall until the mucosa turned white (about thirty seconds). The crystal was removed and 10 per cent alcohol sprayed on the wall. The opening in the ductal wall was not sutured. The icterus index was normal on April 3 and 4 but 100 units on April 10. The dog died on April 24. At necropsy there was leakage from the choledochotomy wound.

2. In dog 87 the common duct was traumatized with phenol. The postoperative recovery was uncomplicated. The icterus index was normal, and the dog was killed on May 1. At necropsy the gallbladder was somewhat larger than normal. The common bile duct was healed and showed no sign of stricture or other deformity.

*Summary and Conclusions.*—Destruction of an area of common duct mucosa by phenol may interfere with healing of the duct, but stricture had not formed after twenty-one days in 1 dog.

SUMMARY

1. A surgical gut ligature on the common bile duct was absorbed and the jaundice cleared.

2. A nonabsorbable ligature can be removed, with relief of the obstruction. Stricture did not follow during the period of observation.

3. Crushing of the common bile duct may be followed by dilatation of the duct, but jaundice did not develop.

4. Complete section of the common duct was not followed by spontaneous healing of the duct. Partial section of the duct, or partial anastomosis after complete section, is usually followed by healing of the duct.

5. Choledochotomy and cauterization of the duct with phenol may or may not be followed by healing of the duct.

# INTUSSUSCEPTION DUE TO FAMILIAL ADENOMA OF THE SMALL INTESTINE

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AMONG the surgical emergencies of the abdomen, intussusception is one of the most urgent, and the relative infrequence of this condition after infancy makes isolated cases in older persons of particular interest to the general surgeon.

Intussusception in the first two years of life is of fairly frequent occurrence, while in the rest of the life span it is peculiarly infrequent. In an analysis of cases of intussusception, Perrin and Lindsay [1] found that of 400, 78.5 per cent occurred in the first two years and 69.75 per cent in the first year of life. Of the type of intussusception occurring in infants, no etiologic factor was apparent in 95 per cent of the cases, while in the form found later in life a definite causative agent usually is found. Dickson [2] stated that intussusception in the adult is always secondary to some underlying condition.

Perrin and Lindsay listed the following causes of intussusception: (1) perverted peristalsis, with retrograde movement of one segment of bowel on another; (2) a paralytic condition of the intestine, allowing prolapse of one portion into another, and (3) the presence of some congenital abnormality, such as a constriction, or some growth, such as carcinoma, acting as the exciting cause. In cases of intussusception in infants in which no obvious mechanism is found, the condition probably is due to perverted peristalsis, paralysis of a segment of the intestine or a congenital constriction ring, or, possibly, as Watts [3] pointed out, it may result from congenital hypermotility of the cecum, allowing ileocolic intussusception to develop. Of the type found after the first two years of life, by far the commonest cause is the presence of a tumor in the bowel.

Tumors of the small bowel have given rise to a considerable amount of writing in recent years, chiefly because of their relative rarity.

From the Surgical Service of Stuart Circle Hospital.

1. Perrin, W. S., and Lindsay, E. C.: Intussusception, Brit. J. Surg. **9**:46, 1921.
2. Dickson, W. B.: Multiple Adenomas of the Jejunum, Ann. Surg. **119**:283, 1944.
3. Watts, L. H.: Intussusception in the Adult, Ann. Surg. **53**:408, 1911.

Usually their presence is discovered only when some complication of their existence has taken place. The commonest causes of their discovery are intussusception, obstruction of the lumen from increasing growth and malignant degeneration. Rankin and Newell,[4] after a survey of benign tumors of the small intestine at the Mayo Clinic, remarked on the rarity of these tumors. Raiford [5] listed as causes of the relative infrequence of tumors in the small bowel (1) the relative freedom from stasis of the small intestine (except in the terminal portion of the ileum, where the incidence of tumors is highest) and (2) the fact that there is little chance for arrested development and misplaced embryonal tissue in the small intestine because it develops chiefly during the last four months of fetal life. Raiford could find only 50 benign tumors of the small intestine in the material of 11,500 autopsies and in 45,000 surgical pathologic specimens at the Johns Hopkins Hospital, and Rankin and Newell reported only 35 cases from the records of the Mayo Clinic.

Pathologically, benign tumors of the small intestine may arise from any of the cells normally present in the intestinal wall. Thus there may be adenomas, fibromas, lipomas, angiomas and myomas. These tumors may be sessile, pedunculated or in the intestinal wall, and all pedunculated tumors may be classified as polyps. The commonest benign tumor of the small bowel is the adenoma. Raiford found 15 adenomas in a series of 50 benign tumors, while at the Mayo Clinic there were 11 adenomas in a series of 35 benign tumors. Willis,[6] however, emphasized the rarity of adenomas, and he found only 19 cases in a series of 7,592 autopsies at the Massachusetts General and Boston City Hospitals up to 1920. Adenomas of the small intestine may occur at any age and in either sex, and they are found oftenest in the lower portion of the small intestine. They are usually single but may be multiple, and they may be sessile or pedunculated. Polyposis is not uncommon in the colon and may be seen in the ileum, and multiple adenomas in the small intestine have been described by Dickson,[2] Brown [7] and Wardill.[8] The tumors vary in size from a few millimeters to a few centimeters in diameter. Section often shows a papillomatous structure with a white pedicle and fibrous tissue permeating the growth and dividing it into

4. Rankin, F. W., and Newell, C. E.: Benign Tumors of the Small Intestine, Surg., Gynec. & Obst. **57**:501, 1933.

5. Raiford, T. S.: Tumors of the Small Intestine, Arch. Surg. **25**:122 (July); 321 (Aug.) 1932.

6. Willis, A. M.: Intussusception Resulting from Benign Tumor of the Intestine, Surg., Gynec. & Obst. **30**:603, 1920.

7. Brown, R.: Invagination Ileus in Polyposis of Small Intestine, Arch Surg. **15**:441 (Sept. 27) 1927.

8. Wardill, W. E. M.: Polypi in the Bowel Causing Intussusception, Brit. J. Surg. **13**:158. 1925.

lobules. The cells have the appearance of those of the intestinal mucosa, but undifferentiation and rapidity of growth are often present at the periphery. The incidence of malignant growths was found by Raiford to be 6.6 per cent, but Doering stated that 45 to 50 per cent of adenomas undergo malignant changes. The vast majority exhibit the uniform glandular structure of the mucosa of the small intestine. The presence of inflammatory cells in the periphery and the association of adenomas with pinworm infection and with colitis have suggested that an inflammatory mechanism is responsible for the development of these tumors, while another theory is that they arise from cell rests or other defects in the mucosa. The symptoms of adenoma of the small intestine are usually those of bleeding or obstruction, and recurring intussusception due to tumor may be the cause of irregular attacks of colicky abdominal pain in adults without obvious cause (Oughterson and Cheever).[9] Polyposis of the small intestine clinically may resemble colitis.

The incidence of intussusception associated with tumors of the small bowel is much greater with benign than with malignant growths. Intussusception was reported by Raiford to have occurred in 23 per cent of his cases, while Rankin and Newell found it in 33 per cent of their series. Staemmler and Joyce[10] both listed an incidence of 30 per cent.

Intussusception as a complication of adenoma of the small intestine has been reported rather frequently in the past thirty years (Brown,[7] Fiske,[11] Cave,[12] Cassidy and Macchia[13] and King[14]). The mechanism of intussusception due to tumor has been well described by Wardill.[8] He postulated two distinct processes: 1. When the tumor is pedunculated, it may be seized by the peristaltic wave and dragged along through the lumen of the bowel, pulling a segment of intestine behind it and causing invagination, with the tumor at the apex of the intussusceptum. 2. The tumor may act as a foreign body and produce a spasmodic contraction of the intestine around it, with inhibition of the part distal to it; "the conditions are now favorable for that act of peristaltic gymnastics whereby the contracted part is induced to slip into the dilated portion," producing intussusception with the tumor elsewhere than at the apex of the intussusceptum.

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9. Oughterson, A. W., and Cheever, D.: Recurring Intussusception Caused by Intestinal Neoplasms, Requiring Multiple Operations for Its Relief, Surg., Gynec. & Obst. **48**:682, 1929.

10. Joyce, T. M.: Tumors of the Small Intestine, Ann. Surg. **100**:949, 1934.

11. Fiske, F. A.: Intussusception Due to Intestinal Tumors, Ann. Surg. **106**:221, 1937.

12. Cave, H. W.: Tumors of the Small Intestine, Ann. Surg. **96**:269, 1932.

13. Cassidy, J. M., and Macchia, B. J.: Polyposis of Duodenum and Jejunum: Report of an Instance, Am. J. Digest. Dis. **1**:755, 1934.

14. King, E. L.: Benign Tumors of the Intestines, Surg., Gynec. & Obst. **25**:54, 1917.

The familial tendency of polyposis of the bowel has been pointed out by Horsley and Keasbey,[15] by Bockus,[16] by Huchtemann,[17] and by Junglung.[18] More specifically, the occurrence of tumors of the small intestine in more than one member of a family has been cited by Gatersleben [19] and others.

The occurrence in more than one member of a family of intussusception of the small intestine due to adenoma is rare and particularly interesting. The cases reported here are instances of this sort.

## REPORT OF CASES

CASE 1.—*First Admission* (quoted from Willis [6]).—"A. K., female, aged 7, admitted to Johnston-Willis Sanatorium on April 6, 1919. The family history is negative. One year prior to admission, the patient had an attack of abdominal pain of great severity, but recovered without being seen by any physician. Three weeks ago, a similar attack occurred, lasting several hours. Again, no physician was called. Three hours before admission, while playing in park, the patient was seized with agonizing abdominal pain, accompanied by nausea and vomiting. The pain was so severe that the child was completely prostrated. Physical examination showed a mass, several inches in diameter and about a foot in length, extending diagonally across the abdomen, just above the umbilicus. A diagnosis of intussusception was made.

"Two hours after admission, the condition being unaltered, operation was advised. Through a midline incision, the mass was delivered and found to consist of an ileal intussusception about two feet in length. [This was found at a later operation to have been jejunal.] The invagination was reduced with great difficulty and . . . a small pedunculated tumor was found at its apex. The serosa over the attachment of the tumor presented a puckered appearance, resembling that sometimes seen in the skin over early carcinoma of the breast. For this reason, it was deemed wise to resect about 6 inches of the small intestine, followed by end-to-end anastomosis. The child was reported fully recovered 8 months after operation.

"*Pathological Report.*—The tumor measured 2 centimeters in length, 1 centimeter in thickness, and 1 centimeter in depth. It was soft, smooth, and pinkish-gray in color, and it was attached to a small portion of the bowel wall by a pedicle which measured one-half centimeter in length and one-half centimeter in thickness. On section it appeared to be lobulated and the lobules varied in size from a pin-point to a pin-head. Microscopic section (transverse) showed the tumor to have gland-like structure, not unlike that seen in normal mucosa. The acini were lined by a columnar epithelium and goblet cells. Some of the acini were cystic and contained mucus. There was a connective-tissue stroma between the gland-like collections of epithelium. Near the pedicle and in the region of its attachment to the bowel wall the acini suggested a malignant degeneration, but there was no apparent invasion of the bowel wall. Diagnosis: adenoma."

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15. Horsley, J. S., and Keasbey, L. E.: Tumors of the Small Intestine, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1943, vol. 6, chap. 17.

16. Bockus, H. L.: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1943, vol. 2, p. 128.

17. Huchtemann, cited by Roan.[21]

18. Junglung, O., cited by Roan.[21]

19. Gatersleben, H., cited by Horsley and Keasbey.[15]

*Second Admission.*—Eighteen years later, on Nov. 2, 1935, A. K., then 25 years old, was admitted to St. Luke's Hospital, complaining of abdominal pain. She had noticed slight pain in the abdomen on the night of November 1, and at 6 a. m. on November 2 she was seized with severe midabdominal pain, which grew steadily worse until the time of admission. There had been no nausea or vomiting. One year previously, she had experienced a similar attack, lasting three days. The past history revealed that the patient had had an intussusception caused by an adenoma in 1919 (see foregoing account). In 1928 she had been hospitalized at the Sheltering Arms Hospital with the diagnoses of chorea, rheumatic endocarditis (mitral) and secondary anemia, and she had received transfusions for anemia. She had been under observation for several years for an unexplained "secondary" anemia, and her hemoglobin reading had fluctuated between 35 and 75 per cent after treatment with iron. She also gave a history of chronic fatigue and had been told by her family that she was lazy.

*Physical Examination.*—On admission the patient was acutely ill and in obvious pain, with an initial temperature of 96.4 F., a pulse rate of 82 and a respiratory rate of 16. The heart was slightly enlarged to the left, and there was a soft systolic murmur at the apex transmitted up along the left border of the sternum, but the rhythm and rate were normal. The abdomen was tense and rigid, with tenderness throughout. No mass was palpable. The urine showed a trace of albumin and gave a 3 plus reaction for acetone. The red blood cell count was 3,900,000, with 51 per cent hemoglobin, and the white blood cell count 13,100, with 90 per cent polymorphonuclear leukocytes and 10 per cent lymphocytes. The preoperative impression was that of intestinal obstruction.

*Operations.*—On November 2, a midline incision was made through the old scar. The colon and appendix were normal. In the left lower portion of the abdomen there was a tremendously distended loop of small bowel which had been invaginated. Just outside this mass there was a scar on the small bowel, which evidently indicated the site of the previous resection. This scar was not adherent, and the lumen was normal. The small bowel was easily reduced, and near the head of the invaginated bowel a tumor, apparently a polyp, about 1½ inches (3.8 cm.) in diameter, was found in the lumen. This tumor did not completely obstruct the bowel. On account of the edema and the fact that the obstruction had been complete for more than twenty-four hours, it was considered wise to postpone resection of this area until the patient had recovered from the obstruction and the bowel had been restored to normal. The wound was therefore closed with sutures of chromic surgical gut U.S.P., silkworm gut and silk.

On November 11, an incision was made in the midline, with excision of the old scar. The entire small bowel was explored. It was normal except for moderate edema in the area which had previously been strangulated. The polyp was again intussuscepted for a distance of about 6 inches (15 cm.), evidently because of the contraction brought on by the spinal anesthesia. The polyp was the only such tumor found in the entire length of the small bowel, and it was attached by a long pedicle. It could be moved freely up and down the bowel for a distance of about 2 inches (5 cm.) on each side. The bowel was opened immediately over the polyp by a transverse incision. The segment of the bowel was excised close to the mesenteric border, to which the pedicle was attached, and the wound closed with continuous sutures of chromic surgical gut and interrupted mattress sutures of fine silk. This point in the bowel was about 3 feet (90 cm.) from the duodenojejunal junction and about 6 inches (15 cm.) from the site of the former resection. The appendix was removed. The wound was closed with sutures of chromic surgical gut U.S.P., silkworm gut and silk.

*Pathologic Report.*—The polyp measured 3 by 3 by 2 cm., and had a cauliflower-like, thick, short pedicle. The growth did not invade the deeper layers of the intestinal wall. Microscopic examination showed it to be made up of intestinal glands of various sizes and in orderly arrangement. The epithelial cells surrounding the glands showed no invasive tendency. The tumor was diagnosed as a benign papilloma of the intestine.

*Progress.*—Recovery from the operations was uneventful, and the patient has since been perfectly well.

CASE 2.—W. G. B. Jr., the 4 year old son of the patient in case 1, was admitted to Stuart Circle Hospital at 2:30 p. m. on March 16, 1947. The child's mother stated that he had awakened at 4 a. m. on the day prior to admission, complaining of severe abdominal pain. Nausea and vomiting followed shortly thereafter, and the pain, although intermittent, continued all that day and night and was present at the time of admission on the following day. Since the onset of the pain, the child had had no bowel movement. Enemas were returned clear without gas, and no blood had been passed per rectum. There was a history of similar, less severe attacks every week for three months prior to admission. Because of anemia, iron had been given for a year, and during this time the stools had been black. The family history was noncontributory except for the mother's intussusceptions.

Physical examination on admission revealed that the child was acutely ill and lying on his right side with the legs flexed on the abdomen. The temperature was 101 F. and the pulse rate 140. The heart and lungs presented nothing remarkable. The abdomen was generally tender. There was a firm mass measuring 2 by 4 inches (5 by 10 cm.) in the midline just above the umbilicus. The mass was very tender, and peristalsis was absent. The red blood cell count was 1,660,000, with a hemoglobin content of 29 per cent. The white blood cell count was normal, as were the results of urinalysis. The preoperative diagnosis was intussusception.

*Operation.*—A paramedian incision was made on the right side. The small bowel was moderately distended. About 300 cc. of straw-colored fluid was encountered in the peritoneal cavity. A mass consisting of 15 inches (38 cm.) of invaginated small intestine was found, and it was thought that this was in the midjejunum. Reduction of the intussusception was attempted and found to be impossible. Resection of the area and end to end anastomosis were performed. The wound was closed in layers. During the procedure the patient received 300 cc. of blood.

After operation the child was extremely ill and was given another transfusion on the day after operation. Supportive treatment consisted of Wangensteen suction, use of penicillin and parenteral administration of fluids. The patient was able to take soft foods by the third postoperative day. Slight atelectasis developed and this was combated with flat hand percussion of the chest and with glucosulfamerazine* (sulfamerazine, 2 Gm., and sodium lactate, 2.24 Gm. per fluidounce [30 cc.] of glucose solution). The wound healed by first intention, and at the time of the patient's discharge the red blood cell count had risen to 4,660,000 and the hemoglobin reading to 85 per cent.

*Pathologic Report.*—The resected segment of bowel measured 98 cm. in length, 45 per cent of which was dark brown. An adenoma measuring 27 by 18 mm. was located at the head of the intussusceptum and showed intense congestion and degeneration. There was no evidence of malignancy.

*Progress.*—Recovery has been complete, and the patient now plays normally and no longer seems to be pale and run down.

COMMENT

The rarity of an instance such as this is attested by the infrequence of reports concerning it. A survey of the literature revealed only 4 other records of intussusception due to familial occurrence of tumors of the small intestine. In a remarkable family reported by Sharber,[20] Roan,[21] Haggard and Floyd[22] and Miller,[23] 3 members underwent multiple operations for intussusception due to adenomas of the small intestine. All told, 9 resections were performed on 3 members of the family (father, son and daughter) for adenomas and intussusception. Van Dijk and Oudendal[24] reported a case of intussusception due to a neoplasm of the small bowel in which the patient's sister also had had a resection for intussusception. Gatersleben[19] described a case of multiple polyposis of the small intestine with repeated intussusceptions and cited 3 similar cases, in all of which a familial history had been obtained. Reisinger[25] cited 1 case in which three operations had been performed on 1 patient for recurring intussusception and in which the father had died seven years before of obstruction of the intestine by a mucous polyp. In addition, MacDermott[26] reported a case of resection of the ileum due to a polyp, in which case the patient's sister had a history of recurrent pain and passage of blood and mucus per rectum. In the cases recorded here, the first admission in case 1 was reported by Willis[6] in 1920.

It should be noted from these case reports that symptoms and signs directly attributable to the presence of the tumors in the small bowel had been present for a considerable length of time without recognition of their true nature. In both cases, multiple attacks of abdominal pain had occurred before the episodes which led to the emergency laparotomy. In both cases, unexplained anemia, with accompanying fatigue, had existed and almost certainly had been due to gastrointestinal hemorrhage, which had been unrecognized.

Dickson[2] emphasized "the obscure nature of the symptoms associated with tumors of the small bowel. These may suggest gallstone colic, renal colic, peptic ulcer, or *even a primary anemia.* Intussusception is a common complication. Celiotomy for intestinal obstruction reveals the true diagnosis often for the first time." Cassidy and Macchia[13] and

20. Sharber, A. L.: Report of a Case of Intussusception, J. A. M. A. **55**:907 (Sept. 10) 1910.

21. Roan, O.: Intussusception Due to Benign Tumors of the Small Intestine, Texas State J. Med. **27**:782, 1932.

22. Haggard, W. D., and Floyd, W. O.: Repeated Resections for Intussusception Due to Familial Tumors of the Small Intestine, Am. J. Surg. **28**:428, 1935.

23. Miller, C. M.: Adult Intussusception, J. Tennessee M. A. **32**:163, 1939.

24. Van Dijk, J. A., and Oudendal, A. J. F., cited by Oughterson and Cheever.[9]

25. Reisinger, cited by Haggard and Floyd.[22]

26. MacDermott, E. N.: Intussusception in the Adult Due to Tumors, Brit. M. J. **1**:1214, 1935.

Raiford [27] stressed the importance of roentgenograms, including the scout film and the gastrointestinal series, in establishing the presence of tumors of the small bowel. These authors, furthermore, emphasized the important differential point of achlorhydria in cases of tumor of the upper portion of the small bowel, in contradistinction to the hyperacidity of peptic ulcer.

In summarizing their paper on recurring intussusception caused by intestinal neoplasms, Oughterson and Cheever [9] listed the following admonitions:

1. Among the possible causes of irregular attacks of colic-like abdominal pain in adults, without obvious etiology, must be counted recurring intussusception.

2. In patients with such symptoms to remove a suspected but innocent appearing appendix, or to fix a harmlessly mobile kidney without careful examination of the intestinal tract, is poor surgery.

3. If an intussusception is found and reduced it is wise to assume that a tumor is present at the apex of the intussusceptum which should be removed.

4. If no tumor is found in connection with the intussusception, search should be made for one a short distance both proximally and distally.

5. If a tumor is found without intussusception, the intestine should be examined proximally and distally as another one may be present there.

6. In any case of intussusception due to tumor, the whole intestinal tract should be examined as thoroughly as possible, since tumors are often multiple and may cause recurrent attacks.

Every tumor of the intestinal tract, especially if the tumor is situated within the lumen of the intestine, no matter how benign the character of the growth, should be removed unless there is definite contraindication, since it always carries the threat of intussusception.

## SUMMARY AND CONCLUSIONS

Intussusception, a relatively rare occurrence after the age of 2 years, is most frequently encountered in later life as a complication of tumors of the small bowel. Benign tumors are commoner than malignant growths in the small intestine; yet they are infrequently found, either clinically or pathologically. Adenoma is the most commonaly encountered benign tumor of the small intestine. Intussusception occurs as a complication in about 30 per cent of cases of tumors of the small bowel.

Intussusception occurring in more than one member of a family as a result of adenoma of the small intestine is an unusual circumstance. Two case histories illustrating this interesting occurrence are presented. In both cases, symptoms directly attributable to tumors of the small bowel were exhibited but were not recognized as such prior to operation for intussusception. The association of recurrent attacks of abdominal pain with secondary anemia should suggest the possibility of tumor of the small bowel. Intussusception in the adult always is secondary to some underlying condition, usually benign tumor of the small intestine.

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27. Raiford, T. S.: Tumors of the Small Intestine, Radiology **16**:253, 1931.

# "EFFORT" THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS

## An Analysis of Sixteen Personal Cases and Fifty-Six Cases Collected from the Literature

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"EFFORT" thrombosis of the axillary, subclavian and, occasionally, brachial veins, although occurring infrequently, may be the consequence of either severe or unaccustomed exertion. This report is an analysis of 72 cases, 16 of which I have collected and 56 of which are assembled from a partial review of the literature [1] for the past ten years.

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1. (*a*) Allin, R. N.: Thrombosis of Axillary Vein Following Effort: A Case Report, Journal-Lancet **61**:47, 1941. (*b*) Barker, N. W.: Axillary Thrombophlebitis Caused by Strain or Effort, Proc. Staff Meet., Mayo Clin. **10**:156, 1935. (*c*) Bruce, N. H.: Primary Axillary Vein Thrombosis: Report of a Case, U. S. Nav. M. Bull. **43**:748, 1944. (*d*) Cohen, H. H.: Strain Thrombosis of the Axillary Vein, J. Bone & Joint Surg. **24**:452, 1942. (*e*) DeBakey, M.; Ochsner, A., and Smith, M. C.: Primary Thrombosis of the Axillary Vein, New Orleans M. & S. J. **95**:62, 1942. (*f*) Ditter, F. J., and Walker, J. H.: Phlebothrombosis of Axillary and Subclavian Veins, Northwest Med. **43**:356, 1944. (*g*) Eigen, L. A.: Thrombosis of the Basilic, Axillary, and Subclavian Veins of Undetermined Origin, J. M. Soc. New Jersey **43**:45, 1946. (*h*) Ffrench, G. E.: Spontaneous Thrombosis of Axillary Vein, Brit. M. J. **2**:277, 1944. (*i*) Friedland, E., and Farber, J. E.: Primary Thrombosis of the Axillary Vein: Case Report, Indust. Med. **10**:247, 1941. (*j*) Goldberg, B. I., and Foley, J. A.: Primary Thrombosis of the Axillary Vein, New England J. Med. **218**:521, 1938. (*k*) Gottesman, J., and Beller, A. J.: Primary Idiopathic Thrombosis of Axillary Vein, Am. J. Surg. **35**:588, 1937. (*l*) Gould, E. P., and Patey, D. H.: Primary Thrombosis of the Axillary Vein: A Study of Eight Cases, Brit. J. Surg. **16**:208, 1928. (*m*) Greenfield, I.: Thrombosis of the Axillary Vein, Ann. Int. Med. **17**:732, 1942. (*n*) Hoffert, H. E.: Thrombosis of the Axillary Vein, Minnesota Med. **25**:664, 1942. (*o*) Kaplan, T.: Thrombosis of the Axillary Vein: Report of Five Cases with Comments on Etiology, Pathogenesis and Diagnosis, J. A. M. A. **10**:2059 (June 18) 1938; (*p*) Thrombosis of the Axillary Vein, Surgery **12**:184, 1942. (*q*) Mason, J. W.: Primary Thrombosis of the Axillary Vein Caused by Strain, Internat. Clin. **1**:239, 1938. (*r*) Matas, R.: On the So-Callel Primary Thrombosis of the Axillary Vein Caused by Strain: Report of a Case with

*(Footnote continued on next page)*

"Effort" thrombosis was first reported in 1884 by von Schrötter.[2] By 1920, Cadenat [3] was able to collect 27 cases. Paggi,[4] in a review of the literature, found only 74 cases reported up to July 1933, and Matas [1r] in 1934 was able to cite 100 such cases. Veal, in 1940,[5] reviewing the literature for the last fifty years, was able to collect less than 150 cases and reported 17 of his own. His statistics are, however, subject to qualification, since he includes types of thrombosis other than "effort" thrombosis in his series. Only 4 cases could be so classified. In 1943 Veal and Hussey [6] reported 29 additional cases of thrombosis, but only 10 were of the traumatic or effort type. Undoubtedly many cases occur that are not reported. It is apparent that the occurrence of "effort" thrombosis of the upper extremity is infrequent clinically. In direct contrast, the incidence of intravenous clotting in the lower extremities is frequent. The literature also reflects the difference in thrombosis of the lower extremities and "effort" thrombosis as regards mortality. This difference hinges chiefly on the problem of pulmonary embolism in thrombosis of the lower extremities, which has been reported to occur in from 0.02 to almost 1.00 per cent of surgical cases.[7]

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Comments on Diagnosis, Pathogeny, and Treatment of this Lesion in Its Medico-Legal Relations, Am. J. Surg. **24**:642, 1934. (*s*) McClanahan, B. V.: Primary Thrombosis of the Axillary Vein, ibid. **30**:459, 1935. (*t*) Oldfield, M. C., and Pyrah, L. N.: Thrombosis of the Axillary Vein, Brit. M. J. **2**:68, 1936. (*u*) Pelner, L., and Cohn, I.: Primary Thrombosis of the Axillary and Subclavian Veins, Am. J. M. Sc. **203**:340, 1942. (*v*) Sampson, J. J.: An Apparent Casual Mechanism of Primary Thrombosis of the Axillary and Subclavian Veins, Am. Heart J. **25**:313, 1943. (*w*) Stabins, S. J.: Primary Thrombosis of the Axillary Vein Due to Strain, U. S. Nav. M. Bull. **41**:1106, 1943. (*x*) Stover, L., and Herrell, W. E.: Extensive Thrombosis of the Right Subclavian and Axillary Veins Associated with Thrombophlebitis, Lymphedema, and Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **15**:817, 1940. (*y*) Willicuts, M. D., and Shelburne, S. A.: Thombosis of the Axillary Vein: Reports of Two Cases with Clinical Investigations, U. S. Nav. M. Bull. **41**:1730, 1943.

2. von Schrötter, L.: Erkrankungen der Gefässe, in Nothnagel, C. W. H.: Handbuch der allgemeinen Pathologie, Berlin, A. Hirschwald, 1884, p. 533; cited by Sampson.[1v]

3. Cadenat, F. M.: Thrombophlebitis of the Upper Extremities, Presse méd. **35**:253, 1920; cited by Eigen.[1g]

4. Paggi, B.: Thrombosi venose da sforzo degli arti superiori, Policlinico (sez. chir.) **40**:383, 1933; cited by Goldberg and Foley.[1j]

5. Veal, J. R.: Thrombosis of the Axillary and Subclavian Veins with a Note on the Post-Thrombotic Syndrome, Am. J. M. Sc. **200**:27, 1940.

6. Veal, J. R., and Hussey, H. H.: Thrombosis of the Subclavian and Axillary Veins: Report of Forty-Six Cases, Am. Heart J. **25**:355, 1943.

7. Barker, N. W.; Nygaard, K. K.; Walters, W., and Priestly, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **15**:769, 1940; **16**:1, 17 and 34, 1941. Heard, J. E.: Postoperative Pulmonary Embolism, in papers of the Mayo Clinic and Mayo Staff, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 419. Wilson, L. B.: Fatal Postoperative Embolism, Ann. Surg. **56**: 809, 1912.

In the upper extremity this complication practically never occurs.[8] It is on this basis that I am convinced that "effort" thrombosis is actually an inflammatory type of reaction in distinction to bland venous thrombosis. Its occurrence is frequently heralded by the marked and dramatic onset of acute vasospasm as exhibited by cyanosis, edema and pain. Its manifestations are more characteristic of a thrombophlebitis with fixation of the thrombus by an inflammatory reaction.[1b]

## INCIDENCE

*Sex.*—The condition occurs principally in males. In the combined series of 72 cases there were only 12 females (16.7 per cent). These figures are weighted since my series was collected from groups consisting entirely of males. Consideration of the 56 cases collected from the literature showed 12 females, increasing the incidence to 21.4 per cent. Only a few cases involving females not included in this series have been reported in the literature.[9]

*Age.*—Although, in accordance with the definition of "effort" thrombosis, the greatest incidence is during the most active periods of life, with the highest peak in the 20 to 29 year age group, the condition can occur at almost any age. It has been reported at the age of 16[1e] as well as at the age of 66.[1x] It is significant that 56 patients were in the most active age groups (10 to 39), accounting for 77.8 per cent of the cases (fig. 1).

*Site of Involvement.*—Since "effort" thrombosis has been alluded to as a type requiring unusual activity or strain, one would expect the right subclavian and axillary veins to be most frequently involved, since most persons are right handed. In the 56 instances collected from the literature the condition was on the right in 37 (66.1 per cent) and on the left in 19 (33.9 per cent). In my series, it was on the right in 10 (62.5 per cent) and on the left in 6 (37.5 per cent) and in the combined

8. (*a*) Moure, P.: Fracture de l'humerus, thrombose de la veine axillaire, embolie pulmonaire, Bull. et mém. Soc. anat. de Paris **89**:170, 1914; cited by Matas,[1r] (*b*) Moure, P., and Martin, R. H.: A'propos de la thrombo-phlébite par effort, Presse méd. **132**:371, 1932. (*c*) Schepelman, E.: Kasuistische Beiträge zur Venenthrombose mit besonderer Berücksichtigung, alterer und neuerer Theorien der Thrombose, Beihefte z. Med. Klin. **7**:23, 1911.

9. (*a*) Finkelstein, B.: Benigne Thrombose der oberen Extremität, Deutsche med. Wchnschr. **53**:198, 1927; cited by DeBakey, Oschner and Smith.[1e] (*b*) Firth, D., and Mackay, R.: Primary Thrombosis of the Axillary Vein with Recurrence, Lancet **2**:679, 1932. (*c*) Rosenthal, W. J.: Ueber Thrombose an der oberen Extremität nach Anstrengungen, Deutsche Ztschr. f. Chir. **117**:405, 1912; cited by DeBakey, Ochsner and Smith,[1e] and by Sampson,[1v] (*d*) Veal, J. R. and McFetridge, E. M.: Primary Thrombosis of the Axillary Vein, Arch. Surg. **31**:271 (Aug.) 1935. (*e*) Winterstein, O.: Traumatic Arterial Spasm and Thrombosis of Subclavian Vein, Schweiz. med. Wchnschr. **55**:360, 1925. Cadenat.[3]

series on the right in 47 (65.3 per cent) and on the left in 25 (34.7 per cent) (fig. 2). Paggi [4] found that the ratio of involvement of the right and the left arm was 2.5 to 1, whereas in this combined series the ratio was less than 2 to 1.

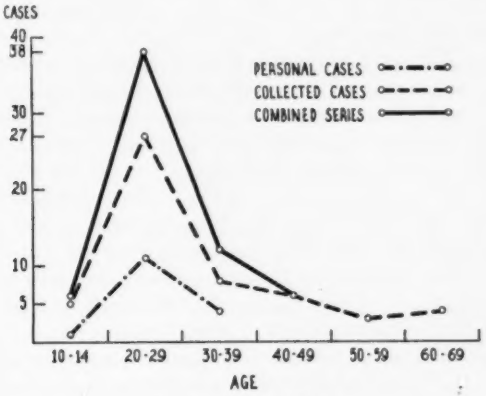


Fig. 1.—Age incidence.

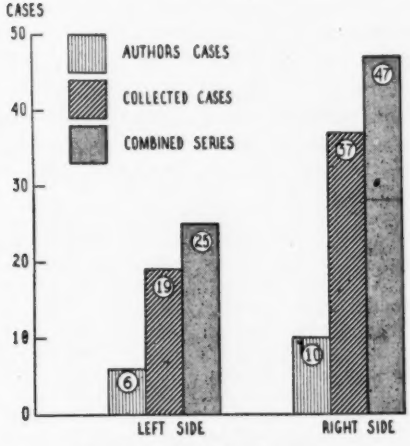


Fig. 2.—Side of involvement.

## INCITING INCIDENT

Although the inciting or predisposing incident has been variously reported, it appears related to some unaccustomed strain or effort. However, there is a large group of cases in which no direct association,

such as pain, occurs between the effort and the thrombosis. This has been called idiopathic or spontaneous thrombosis, but it is probably related to effort, for most of the patients, when closely questioned, will relate some unaccustomed activity preceding the thrombosis. This occurred in 15 of the collected cases [10] and in 8 of my series, making a total of 23 among 72 (31.9 per cent). Additional reports of such occurrence have been made in the literature.[11] In the collected series throwing a baseball [12] was the next most frequently related action precipitating the thrombosis. This often incited a severe thrombosis of the effort type and occurred in 4 of the combined series (5.6 per cent of 72). A cause of additional magnitude was the lifting of heavy objects, which occurred in 4 of the collected cases [13] (7.1 per cent of 56) and in none of mine. The action varied from lifting a pail to lifting a heavy chunk of ice. This has also been reported in the literature elsewhere.[14] Heavy work preceded the thrombosis in 2 cases.[15] Infection of the upper respiratory tract was related to the thrombosis in 2 instances,[16] as was strenuous exercise in the gymnasium.[1b] Other inciting factors occurring in 1 case each were as follows: pitching hay [1b]; pitching soybeans [1s]; strenuously pulling on a wrench [1w]; breaking concrete with a sledge hammer [1y]; epilepsy attack [1y]; housework [1v]; sawing, planing and lifting wood [1v]; swimming [1a]; sawing a tree overhead [1e]; beating time with a baton [1e]; sawing wood [1e]; a fall on the hand [1o]; pushing a heavy object [1p]; basketball [1p]; direct trauma to the shoulder [1u]; sudden flexion of the elbow and backward pushing of the shoulder when a clutch slipped on the lever of a dredge [1b]; alcoholic bout [1b]; tennis [1b]; sudden forceful flexion of the arm when a wrench slipped [1r]; a fall of 30 feet (10 meters) [1d]; golf [1l]; using an electrical cutting machine [1i]; working with a hammer [1l]; putting in screws for curtain rods above the head [1l]; placing jars on a shelf above the head [1l]; cleaning a ceiling [1l], and a test of strength.[1n]

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10. DeBakey.[1e] Ditter and Walker.[1f] Eigen.[1g] Ffrench.[1h] Friedland and Farber.[1j] Goldberg and Foley.[1j] Gottesman and Beller.[1k] Gould and Patey.[1l] Kaplan.[1o] Oldfield and Pyrah.[1t] Pelner and Cohn.[1u] Sampson.[1v] Kaplan.[1p]

11. (*a*) Pellot, J.: Les thromboses veineuse du membré supérieur droit, Presse méd. **11**:264, 1912; cited by Sampson.[1v] (*b*) Routier: Oedème subaigu du membré supérieur, Bull. et mém. Soc. de chir. de Paris **39**:1003, 1913; cited by Sampson.[1v] (*c*) Willan, R. J.: Three Cases of Axillary Vein Obstruction, Edinburgh M. J. **20**:105, 1918. Veal.[5]

12. Hoffert.[1n] Kaplan.[1o] Mason.[1q] Sampson.[1v]

13. Kaplan.[1o] Kaplan.[1p] Stover and Herrell.[1x]

14. Broca: Oedème subaigu du membré supérieur, Bull. et mém. Soc. de chir. de Paris **39**:1004, 1903; cited by Sampson.[1v] Winterstein.[9e]

15. Bruce,[1c] Gould and Patey.[1l]

16. Goldberg and Foley.[1j] Greenfield.[1m]

17. LeRiche, R: Traitement chirurgical des suites éloignées des phlébites et des grands edèmes non médicaux des membrés inférieurs, Bull. et mém. Soc. nat. de chir. **53**:187, 1927; cited by DeBakey, Ochsner and Smith.[1e]

In my cases the causes were as follows: carrying a pack (2 cases) and (1 case each) climbing a rope, throwing rocks, pulling a propeller, a parachute jump, compression of the axilla with a figure-of-8 bandage for clavicular fracture and working with a wrench.

Additional etiologic agents reported in the literature are holding a high-spirited horse [18]; holding back a team of horses [19]; rowing a boat [11e]; struggling to hold an arrested person [20]; pulling up in bed [21]; loading and unloading a piece of field artillery [22]; long stirring of a heavy pudding mixture [9b]; scrubbing clothes for a long time [5]; carpentry work [9e]; throwing a ball or rock [23]; exercises of elevating arms overhead [24]; sleeping with the arms extended upward under the head [8]; moving heavy furniture [25]; pulling tents from trees,[26] and falling on the abducted arm.[27]

It would thus appear that although thrombosis of the axillary and subclavian veins can occur without apparent cause several conditions are conducive to its occurrence. These are principally some form of effort such as lifting, prolonged ordinary activity involving the arm or arms and shoulder girdle, strenuous physical activity involving these same structures, abduction of the arm such as in overhead activity, compression of the shoulder girdle and sudden violent backward motion of the shoulder girdle. The condition has also been described as occurring after disease such as pulmonary tuberculosis [28] and influenza.[29]

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18. Schepelmann, E.: Demonstration eines Patienten mit Thrombose der linken Vena subclavia seltener Aetiologie, München. med. Wchnschr. **57**:2444, 1910; cited by Sampson.[1v]

19. Schwartz, E.: Oedème subaigu du membré supérieur, Bull. et mém. Soc. de chir. de Paris **39**:1002, 1913; cited by Sampson.[1v]

20. Delbet, P.: Oedème subaigu du membré supérieur droit, Progrès méd. **33**:186, 1918; cited by Sampson.[1v]

21. McGoogan, L. A., and Simmons, E. E.: Effort Thrombosis of Axillary Vein in Puerperium, Nebraska M. J. **18**:289, 1933.

22. Murad, J.: Phlébite par effort du membré supérieur, Bull. et mém. Soc. de chir. de Paris **39**:1001, 1913; cited by Sampson.[1v]

23. Finkelstein.[9a] Rosenthal.[9c]

24. Clute, H. M.: Idiopathic Thrombosis of the Axillary Vein, S. Clin. North America **11**:253, 1931.

25. Baum, H. L.: Die traumatische Venethrombose an der oberen Extremität, Deutsche med. Wchnschr. **39**:997, 1913.

26. Schwindt, J. K.: Traumatic Thrombosis of the Upper Extremities, California & West. Med. **27**:635, 1927.

27. (*a*) Lahaussois, M.: Thrombophlébite traumatique aseptique, Presse méd. **18**:410, 1910. (*b*) Lowenstein, P. S.: Thrombosis of the Axillary Vein: An Anatomic Study, J. A. M. A. **82**:854 (March 15) 1924.

28. Blumer, G.: Report of Four Unusual Cases of Peripheral Venous Thrombosis, Yale M. J. **15**:296, 1908.

29. Jakobson, S.: Ueber einen Fall von Thrombose der Vena axillaris nach Influenza, München. med. Wchnschr. **78**:1017, 1931.

PATHOGENESIS

The interpretation of the pathogenesis is subject to a remarkable amount of confusion and will be reviewed only for the sake of completeness. This has been reported comprehensively by Eigen.[1g]

Thrombosis may be precipitated by the following factors.

1. Phlebitis due to sudden stretching and compression of the vein.[30]

2. Rupture of the subclavius-axillary valve in the vein under the subclavius muscle (due to increase in venous pressure) by the sudden stretching of the subclavius muscle with the arm in abduction.[11]

3. Damage to endothelium caused by distention of the axillary veins resulting from respiratory effort.[31]

4. Injury to the intima as a result of pressure on the vein from the coracoid ligament and subclavius muscle with the arm extended and abducted.[27b]

5. Irritation of the perivenous sympathetic plexus, resulting in vasospasm and thrombus formation.[32]

6. Local venospasm resulting from stimulation of the sympathetic neurons, this being the end result of a reflex disorder.[33]

7. Chemical changes in the blood, caused by catabolites of abnormal metabolism in addition to whatever mechanical factors may be involved.[34]

8. Constriction of the subclavius vein below the head of the humerus and against the subscapularis muscle in hyperabduction of the arm.[5]

9. Stimulation of sympathetic nerve fibers resulting in a vasospasm of all corresponding blood vessels (both large and small). This stimulation is a reaction to a great many types of peripheral injuries.[25]

10. Thrombus formation resulting from compression of the subclavian vein produced by a posterior and cephalad rotation of the shoulder girdle without abduction of the arm.[35]

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30. Von Schrötter.[2] Willan.[11c]

31. Cadenat.[3] Lahaussois.[27a] Veal and McFetridge.[9d]

32. (*a*) Cottalorda, J.: La thrombo-phlébite par effort, Lyon chir. **29**:169, 1932; cited by DeBakey, Ochsner and Smith.[1e] (*b*) Hammann, W.: Zur Kenntnis der sogenannten Achselvenen Thrombose, Zentralbl. f. Chir. **67**:1871, 1940. (*c*) Löhr, W.: Ueber die sogenannte traumatische Thrombose der Vena axillaris und subclavia, Deutsche Ztschr. f. Chir. **214**:263, 1929; cited by De Bakey, Ochsner and Smith.[1e]

33. Homans, J.: Vasomotor and Other Reactions to Injuries and Venous Thrombosis, Am. J. M. Sc. **205**:313, 1943.

34. Löhr.[32c] Rosenthal.[9c]

35. Sampson, J. J.: Thrombosis of the Subclavian Vein, Am. Heart J. **19**:292, 1940. Sampson, J. J., and Capp, C. S.: Compression of the Subclavian Vein by the First Rib and Clavicle with Special Reference to the Prominence of Chest Veins as a Sign of Collateral Circulation, Am. Heart J. **25**:303, 1943. Sampson, J. J.; Saunders, J. B. de C. M., and Capp, C. S.: Compression of the Subclavian Vein by the First Rib and Clavicle, with Special Reference to the Prominence of Chest Veins as a Sign of Collateral Circulation, ibid. **19**:292, 1940. Sampson.[1v]

11. Hematoma in the axillary region compressing the axillary vein.[36]

12. Rupture of the intima or tears of small lateral vessels at the mouth of their collaterals by muscular action, based on the premise that the lesion is not situated primarily in the axillary or subclavian veins because their elasticity protects them from injury.[11a]

13. Theory of infection.[37] This is denied, since in some instances in which thrombectomy was done and the thrombus cultured organisms were not found.

14. Undue tightening (stretching) of the vein.[38]

DURATION OF TIME FROM PRECIPITATING EVENT TO MANIFESTATIONS

From a reviewing of the interval between the injury or precipitating event and the onset of symptoms and signs in 27 cases in which this

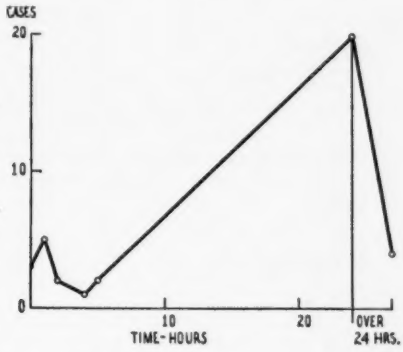


Fig. 3.—Duration of time from precipitating event to onset of manifestations.

was stated (fig. 3), it is evident that the majority occurred in the first twenty-four hours (23 cases, 85.2 per cent). In 10 (37 per cent) the onset was within one hour, and in 3 of these it was immediate. In only 4 did the onset occur after twenty-four hours.

36. Benda, cited by Löhr: Ueber die sogenannte traumatische Thrombose der Vena axillaris und der subclavia, Deutsche Ztschr. f. Chir. **214**:263, 1929. Moure and Martin.[8b]

37. (*a*) Chifolian, M., and Folliasson, A.: Thrombo-phlébite à streptocoques due membré supérieur droit, Presse méd. **40**:84, 1932; cited by DeBakey, Ochsner and Smith.[1e] (*b*) Grimaud and Dandelot: Pathogénie de la thrombo-phlébite dite par effort, Presse méd. **1**:108, 1924; cited by De Bakey, Ochsner and Smith.[1e] (*c*) Lecène, cited by Matas.[1r] Lenormant, C. and Mondor, H.: Sur la prétendue; thrombo-phlébite par effort, Presse méd. **2**:1669, 1931.

38. Triepel, H., cited by Benninghoff, A., in Möllendorff, W. V.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 6, pp. 1 and 130, and by Franklin, K. J.: A Monograph on Veins, Springfield, Ill., Charles C Thomas, Publisher, 1937, p. 324.

### SYMPTOMS

The heralding symptoms were recorded in 51 of the collected cases and are noted in the author's 16 cases (table 1). Swelling was not only the most common heralding manifestation (35.8 per cent) but was also the most frequent on the patients' admission to the hospital, occurring in 61 cases (84.7 per cent). Pain initiated the occurrence of "effort" thrombosis in 32.8 per cent of cases and was likewise the second

TABLE 1.—*Heralding Manifestations (51 Collected Cases and 16 Personal Cases)*

| Symptom | No. | % |
|---|---|---|
| Swelling | 24 | 35.8 |
| Pain | 22 | 32.8 |
| Cyanosis | 4 | 6.0 |
| Numbness | 3 | 4.5 |
| Prominent superficial veins | 3 | 4.5 |
| Aching | 2 | 3.0 |
| Discomfort in axilla and shoulder | 2 | 3.0 |
| Stiffness | 1 | 1.5 |
| Tightness | 1 | 1.5 |
| Tiredness | 1 | 1.5 |
| Soreness of arm muscles | 1 | 1.5 |
| Redness of extremity | 1 | 1.5 |
| Sensation of something giving in the arm | 1 | 1.5 |
| Coldness of the extremity | 1 | 1.5 |

TABLE 2.—*Symptoms on Admission to the Hospital*

| Symptom | No. | % |
|---|---|---|
| Swelling | 61 | 84.7 |
| Pain | 36 | 50.0 |
| Cyanosis | 27 | 37.5 |
| Prominent superficial veins | 19 | 26.4 |
| Numbness | 12 | 16.7 |
| Recurrences | 10 | 13.9 |
| Aching | 9 | 12.5 |
| Stiffness | 8 | 11.1 |
| Weakness of extremity | 6 | 8.4 |
| Tenderness in axilla | 5 | 6.1 |
| Paresthesia (tingling, burning) | 5 | 6.1 |
| Heaviness | 4 | 5.6 |
| Tightness | 4 | 5.6 |
| Thrombosed cord in axilla | 3 | 4.2 |
| Easy fatigability of extremity | 2 | 2.8 |
| Redness of extremity | 2 | 2.8 |
| Soreness | 2 | 2.8 |
| Coldness | 2 | 2.8 |
| Fever | 1 | 1.4 |
| Tender vein | 1 | 1.4 |

most frequent symptom on the patients' admission to the hospital (50 per cent). This parallelism is continued in the instance of cyanosis, which was the third most frequent heralding manifestation (6 per cent) and the third most common manifestation when the patients were first seen (37.5 per cent). Prominence of the superficial veins was the fourth most common initiating sign of thrombosis (4.5 per cent), as well as the fourth most common symptom (26.4 per cent). Numbness was of equal frequency (4.5 per cent) as an initial sign but was only fifth in frequency (16.7 per cent) of the manifestations when the patients were first seen. Discomfort in the axilla and shoulder and aching were of

equal prominence. Other heralding manifestations were stiffness, tiredness, tightness, soreness of the arm muscles, redness of the extremity, coldness of the extremity and the sensation of something giving in the arm.

### EXAMINATION

A consideration of the physical examination in the combined series discloses that swelling was present in all the cases, with brawny edema present in 1 case [1c] (table 3). Other signs occurring in order of frequency are prominent superficial veins, cyanosis, palpable venous cord, coolness on the involved side, tenderness over the involved vein, fulness over the anterior part of the chest and shoulder and rubrocyanosis.

TABLE 3.—*Symptoms Noted on Physical Examination*

| Symptom | No. | % |
|---|---|---|
| Swelling (brawny edema in 1 case) | 72 | 100 |
| Prominent veins | 54 | 76.4 |
| Cyanosis | 29 | 40.3 |
| Palpable venous cord | 23 | 31.1 |
| Cooler on the involved side | 9 | 12.5 |
| Tender over axillary vein | 8 | 11.1 |
| Rubrocyanosis | 6 | 8.4 |
| Fulness over anterior region of the chest and shoulder girdle | 6 | 8.4 |
| Mottled skin | 4 | 5.6 |
| Lividity | 4 | 5.6 |
| Pitting edema | 4 | 5.6 |
| Fever | 3 | 4.2 |
| Rubor | 3 | 4.2 |
| Weakness of extremity | 3 | 4.2 |
| Warmer on involved side | 2 | 2.8 |
| Induration | 2 | 2.8 |
| Tenderness | 2 | 2.8 |
| Pallor on elevation | 2 | 2.8 |
| Lymphadenopathy | 1 | 1.4 |
| Dry skin | 1 | 1.4 |
| Limited motion | 1 | 1.4 |
| Ecchymosis | 1 | 1.4 |
| Congestion | 1 | 1.4 |
| Sweating | 1 | 1.4 |

### SPECIAL EXAMINATION

Oscillometric determinations showed no notable variations, although 1 patient reported on in the literature stated that there was some diminution on the involved side.[1d]

Infra-red photographs merely confirmed the gross clinical findings.

Venous pressure was reported as greater on the involved side in 10 cases in which it was recorded. Venous pressure increasing with exercise, as reported by Veal and Hussey [39] in some cases, was recorded.[1y] This is substantiated by delayed emptying time of veins on elevation. This was confirmed in my cases.

Cutaneous absorption of sodium chloride was equal bilaterally in the case reported in the literature.[1y]

39. Veal, J. R., and Hussey, H. H.: The Use of Exercise Tests in Connection with Venous Pressure Measurements for the Detection of Venous Obstruction of the Upper and Lower Extremities, Am. Heart J. **20**:308, 1940.

Blood sugar and carbon dioxide contents, determined in each extremity by Greenfield,[1m] proved to be equal bilaterally. Bronchoscopy was also performed in this case and revealed no abnormality. Oxygen saturation of the blood was first reported to be lower on the involved side by Horton.[40] This is also recorded by Pelner and Cohn [1u] and by Greenfield.[1m]

Other findings are recorded in a case of polycythemia vera by Stover and Herrel [1x] but are merely in keeping with this diagnosis.

In the present series determinations with the thermocouple done in the subsided stage showed the skin to be warmer on the involved side in 4 cases, although studies in the more acute stages reveal decreased temperature, indicating considerable vasospasm. This varies with the amount of superficial circulation. Sedimentation rates, clotting times and bleeding times proved to be uniformly normal.

A sterile blood culture is reported in 1 case.[1l] The blood pressure was recorded in 6 of the collected cases [41]; in 3 the blood pressure was higher on the involved side, in 2 it was equal and in 1 it was lower. In the present series the incidence of increase and equality was approximately equal. This indicates that in a substantial number of cases there is an elevation of blood pressure on the involved side. Circulation time was recorded in 9 of the collected cases and has been determined in 9 of the present series. In every instance there was a delay of arm to tongue time on the involved side.

Phlebograms were reported in 19 of the collected cases and have been made in the present series as confirmatory of the clinical diagnosis of venous thrombosis. This is done by injecting 15 cc. of 35 per cent iodopyracet injection (diodrast®) into the antecubital vein and making a 14 by 17 inch (35.5 by 43 cm.) roentgenogram of the area under the arm and shoulder extending to the midline. A film should be exposed at this time and the injection continued, 15 cc. more being given and then another film exposed. A Buckey technic is the simplest method. In these circumstances the diagnosis is not difficult provided certain primary etiologic agents are excluded as primary causes.

## DIAGNOSIS

The cardinal points in the diagnosis are as follows:

1. The history of unaccustomed or severe effort.

2. Initial manifestations of swelling and/or pain with cyanosis, prominence of superficial veins, numbness, coldness of the extremity, discomfort in the shoulder or aching.

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40. Horton, B. T.: Primary Thrombosis of the Axillary Vein, J. A. M. A. **96**:2194 (June 27) 1931.

41. Allin.[1a] Cohen.[1d] Ditter and Walker.[1f] Kaplan[1p] Matas.[1r] Sampson.[1v]

3. Swelling, prominence of superficial veins, cyanosis, palpable venous cord (may be tender), coolness on the involved side, tenderness over the vein or fulness over the anterior part of the chest.

4. Increased venous pressure.

5. Delayed circulation time.

6. Phlebographic evidence of venous obstruction.

In the differential diagnosis the following must be considered:

1. Thrombosis as part of a general disease: pyemia, septicemia, puerperal fever, typhoid, gout, polycythemia vera or heart disease.

2. Substernal goiter.

3. Mediastinal and intrathoracic tumors.

4. Aneurysms.

5. Cervical ribs.

6. Syringomyelia.

7. Central or peripheral neuropathic disorders.

8. Local external pressure.

It is obvious that these factors should be excluded as causes of thrombosis.

### TREATMENT

The treatment (table 4) of this form of thrombosis was varied, with rest in bed and elevation of the extremity being the most commonly employed methods. Stellate sympathetic ganglion block was used in 14 cases to treat the vasospasm, which frequently develops as a severe primary manifestation with pain, coldness, cyanosis and even numbness. Another method employed to relieve vasospasm was heat applied to the extremity. DeBakey, Ochsner and Smith [1e] used sympathetic ganglion block in 4 cases with excellent results. Bruce [1c] favored this treatment. Barker,[1b] in reporting 6 cases, felt that during the acute stage simple treatment by rest, elevation of the arm and local hot moist packs is all that is indicated. This may be followed by the use of elastic compression bandages and graded exercises.

Foci of infection in dental and sinus locations were found in 3 of the present cases and removed. This is recommended by Oldfield and Pyrah.[1t]

Regional sympathetic ganglion block was utilized in the late cases, and although there was relief of the cyanosis and discomfort, there was no change in the edema. Other forms of treatment suggested have been multiple incisions,[42] needling to allow the edema to subside, throm-

42. Wilson, G.: Brachial Monoplegia Due to Thrombosis of Subclavian Vein, Am. J. M. Sc. **163**:899, 1922.

bectomy [43] and excision of the thrombotic segment.[44] The location of the thrombus may be in the subclavian, axillary, brachial and even jugular vein. By phlebography Pelner and Cohn [10] showed the thrombosis to be in the subclavian vein at the inner border of the first rib in most cases. Veal [5] stated that in most instances the thrombosis involves the entire axillary vein, portions of the subclavian, basilic and brachial veins and occasionally the external jugular and the internal jugular vein. Roelsen [45] collected 24 cases (3 of his own) in which the axillary vein was explored, and 12 (50 per cent) showed no evidence of thrombosis. Operative removal of the thrombus has been recommended by some [46] to facilitate more rapid recovery, but this has not been borne out by the experience of others. Stabins [1w] favored its removal since, if allowed

TABLE 4.—*Types of Treatment*

| Treatment | Literature | Present Series | Combined |
|---|---|---|---|
| Rest | 19 | 7 | 26 |
| Elevation | 15 | 6 | 21 |
| Stellate block | 6 | 8 | 14 |
| Hot packs | 8 (6 moist) | 4 (moist) | 12 |
| Compression (usually elastic) | 8 | 4 | 12 |
| Ice packs | 1 | 2 | 3 |
| Physical therapy | 1 | 1 | 2 |
| Bronchoscopy | 1 | 1 | 2 |
| Massage | 1 | 1 | 2 |
| Sulfathiazole | 2 | 0 | 2 |
| Calcium lactate orally | 2 | 0 | 2 |
| Immobilization | 2 | 0 | 2 |
| Resection of axillary vein | 1 | 0 | 1 |
| Airplane splint | 1 | 0 | 1 |
| Alternate elevation and dependency | 1 | 0 | 1 |
| Infra-red irradiation | 1 | 0 | 1 |
| Exploration | 1 | 0 | 1 |
| Phlebotomy (case of polycythemia vera) | 1 | 0 | 1 |
| Cast | 1 | 0 | 1 |

43. Bazy, L.: Thrombose de la veine axillaire droite (thrombophlébite dite par effort): Phlébotomie; ablation des caillots; suture de la veine, Bull. et mém. Soc. nat. de chir. **52**:529, 1926. Biebl, M.: Thrombektomie bei blander Thrombose der Vena axillaris und subclavia, Zentralbl. f. Chir. **66**:1560, 1939. Lawen, A.: Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, Zentralbl. f. Chir. **64**:961, 1937; cited by DeBákey, Ochsner and Smith.[1e] Schepelmann.[18]

44. Delbert, M.: Sur les thrombo-phlébites, Presse méd. **21**:549, 1913; cited by DeBakey, Ochsner and Smith.[1e] Huard, P. and Lenormant, C. H.: Un cas de thrombo-phlébite du membré supérieur révélée par un effort: Resection du segment veineux thrombosé et denudation arterielle; guérison, Presse méd. **41**:1946, 1933; **42**:556, 1934; cited by DeBakey, Ochsner and Smith.[1e] Paggi, B.: Un raro caso di thrombosi della vena ascellare destra (thrombosi venose da sforzo), Arch. ed. atti d. Soc. ital. di chir. **39**:998, 1933; cited by DeBakey, Ochsner and Smith.[1e]

45. Roelsen, E.: So-Called Traumatic Thrombosis of the Axillary and Subclavian Veins, Acta med. Scandinav. **98**:589, 1939.

46. Grimault, L., and Dantlo, M.: Thrombophlébite dite par effort de la veine axillaire, Bull. et mém. Soc. de chir. de Paris **50**:118, 1924; cited by Sampson.[1v] Matas.[1r] Paggi.[4] Stabins.[1w]

to remain, the thrombus promotes future infection and "serious complications."

The end results of treatment are disappointing, although initial treatment of vasospasm may be dramatic. In 56 cases in which the results were stated only 13 patients had no residual effects (23.2 per cent). Residual swelling was a most prominent feature, with dilated superficial veins and considerable increase in swelling and discomfort on strenuous or unaccustomed activity. Several patients had to change their occupation. Recurrences are frequent, and in this series they were found in 10 cases (13.9 per cent). These may occur as late as after six years.[25] However, in many instances the swelling begins to subside after several weeks, the collateral venous circulation is soon established and the patient is fit to resume his old activities. Obviously the severity of the residual symptoms depends on the degree of preservation of collateral circulation.[5] In a series of 9 cases reported by Veal,[8] residual symptoms including weakness, early fatigue and pain in the arm after prolonged work or exercise occurred in 7. Sixteen patients observed by me all showed residual swelling, and only 2 were asymptomatic on activity.

Anticoagulants would seem to be of no value in the treatment of "effort" thrombosis, since the thrombosis establishes its full extent at once, and there is little tendency toward progression and practically none toward pulmonary embolism.

## REPORT OF CASES

Case 1 (axillary thrombosis).—S. L. was a physician, white, aged 37 years. In November 1942, while he was playing handball, pain and swelling of the right upper extremity suddenly developed, which subsided spontaneously within five days. In January 1944 he noted recurrence of the discomfort of the right upper extremity with swelling after a volleyball game. Roentgenograms taken at that time disclosed a benign bone cyst in the neck of the right humerus. The swelling and pain were aggravated by exercise, and he even noted tiredness of the extremity after writing for three to four minutes. He also observed tingling paresthesia with numbness. The condition gradually became worse. After discontinuance of the exercise, the pain and swelling subsided. It recurred each time he attempted active exercise. He was first seen by me on Feb. 18, 1945. By this time it was noted that the swelling was continuous, being greater on activity and dependency and in hot weather. The extremity was enlarged, the arm being 1¾ inches (4.4 cm.) larger in circumference, the forearm ½ inch (1.27 cm.) larger and the wrist ¼ inch (0.64 cm.) larger. There was notable dilatation of the superficial vessels. No arterial insufficiency was evident. The thrombosed vein was not palpable. The sedimentation rate was 12 mm. in 1 hour. Clotting time (Lee and White) was 9 minutes and bleeding time 1½ minutes. The venous pressure in the veins in the antecubital space was 28 cm. of water on the right and 17 cm. on the left. The arm to tongue circulation time, with injection of 3 cc. of 10 per cent calcium gluconate rapidly through a 19 gage needle, was 15 seconds on the right and 5 seconds on the left. Roentgenograms of the cervical region of the spine disclosed no cause for the thrombosis, and there was no cervical rib or evidence of scalenus anticus

syndrome. Phlebography (fig. 4*A*) confirmed the diagnosis of axillary thrombosis. Examination for foci of infection in the teeth, ear, nose and throat presented no positive findings. The cyst in the humerus proved to be small, and the orthopedic consultants felt that treatment was not indicated. Stellate ganglion block with procaine hydrochloride was performed three times, resulting in improvement of the edema of the extremity. However, the patient proved to be partially disabled.

Case 2 (axillary thrombosis).—A. T., aged 36, Negro, noticed pain and swelling of the right forearm in October 1944, while cooking. In three weeks' time the swelling had increased to the point where he was unable to button his sleeves, and it had extended to the shoulder. He had been receiving antisyphilitic therapy intravenously, and this may have been a factor. He also noted paresthesia, with weakness of the grip. On initial examination there was a 3 to 4 cm. enlargement of the extremity, with prominent engorgement of the superficial veins. Venous pressure was 38 cm. of water; blood pressures were equal, and circulation time was 20 seconds on the right and 12 seconds on the left with the use of calcium gluconate. A diagnosis of thrombosis of the

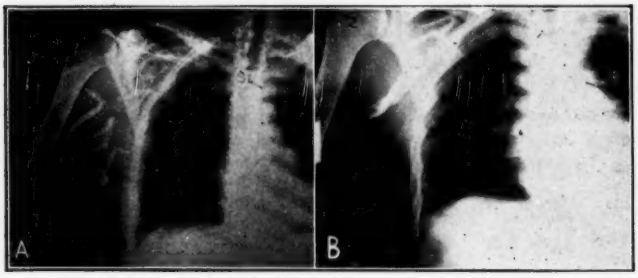


Fig. 4.—Thrombosis of the right axillary vein. *A*, case 1; *B*, case 2.

subclavian vein was made after phlebographic studies. Treatment at that time consisted of elevation of the arm, local application of heat and rest. This resulted in gradual improvement.

He was first seen by me in January 1945, when there was no apparent enlargement of the extremity, although there were some dilated veins present in the arm and several across the shoulder girdle. The sedimentation rate was 2 mm. in 1 hour. At this time he complained of some aching in the right shoulder. A phlebogram (fig. 4*B*) made with iodopyracet injection (diodrast®) showed axillary obstruction. There was no evidence of a focus of infection. By Jan. 25, 1945, the venous pressure was 29 cm. on the right and the circulation time, with 3 cc. of calcium gluconate injected rapidly, was 10 seconds on the right and 12 seconds on the left. This case is a good example of almost complete recovery from axillary thrombosis.

Case 3 (bilateral thrombosis of the subclavian vein).—C. was a white man, aged 36 years, whose first thrombosis was of the right subclavian vein. In 1943, twenty-four hours after he received vaccinations for overseas duty in the army, redness, swelling and pain developed in the right arm and forearm. In the succeeding four days he noted progressing pain, swelling and heat involving the right forearm and wrist. He was treated with infra-red rays to the extremity and rest. Within one month he seemed to have recovered. This resulted in his separation from the service in the early part of 1944.

The second thrombosis, involving the left subclavian vein, occurred in 1947. Six days previous to his admission to the Veterans Hospital, Dallas, Texas, while on duty as a machinist's helper, he noted the sudden onset of numbness and tingling in his entire left upper extremity. The day before he had worked rather hard for a period of thirteen hours repairing a boiler. He noted progression of his symptoms as well as superficial venous distention, with some bluish discoloration of the extremity. Examination disclosed bilaterally distended superficial veins. These remained distended in a horizontal position on the left but collapsed on the right. The axillary vein was distended and tender. The left extremity was ¾ inch (1.9 cm.) larger than the right. The blood pressure was 106 systolic and 60 diastolic on the right and 95 systolic and 54 diastolic on the left. The temperature of the skin was the same on the two sides. Venous pressure was 11 cm. on the right and 21 cm. on the left. Circulation time, with the use of 50 per cent magnesium sulfate, was 40 seconds on the right and 52 on the left. The extremity was elevated and stellate sympathetic ganglion block done, with improvement. Roentgenograms of the shoulder region and the chest, including an esophagram, were taken to rule

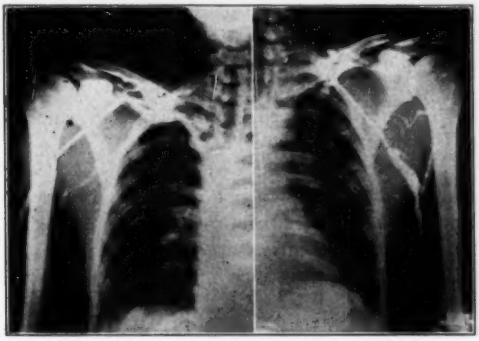

Fig. 5.—Bilateral thrombosis of the subclavian vein in case 3.

out other causes of venous thrombosis. A phlebogram (fig. 5) demonstrated bilateral thrombosis of the subclavian vein. The sedimentation rate, bleeding and clotting times and blood count were normal. The patient was instructed to refrain from severe manual labor and to use a compression bandage whenever the extremity became swollen.

## COMMENT

"Effort" thrombosis of the axillary and subclavian veins occurs predominantly in males (83.3 per cent) in the active age group (77.8 per cent) and most commonly involves the right side (65.3 per cent). The inciting incident may merely be unaccustomed activity (31.9 per cent), pitching a baseball (5.6 per cent) or lifting heavy objects (5.6 per cent). It would appear that prolonged ordinary activity involving the arm or arms and the shoulder girdle, strenuous physical activity involving the same structures, abduction of the arm such as in overhead activity, compression of the shoulder girdle and sudden violent backward motion

of the shoulder girdle are additional factors. The pathogenesis of the condition has been outlined, and it is probable that several factors are acting simultaneously. Swelling (35.8 per cent) and pain (32.8 per cent) are the most frequent heralding manifestations. The swelling is usually gradual and unnoticed at first when a heralding manifestation, whereas the pain is sharp and severe as an initial symptom and is followed by swelling and cyanosis in from one-half to several hours. The swelling usually disappears by the tenth day, having become more severe by the third day. The introductory pain is usually in the shoulder and axilla and rarely along the course of the vein. In contradistinction to what occurs in thrombosis of the lower extremities, in which the distal portion of the extremity tends to swell initially, the most pronounced swelling is in the proximal portion, although the entire extremity may be involved. This swelling may be as much as 3 inches (7.6 cm.).[1t] The initial symptoms must be due to spasm and obstruction. As soon as the spasm subsides and the collateral circulation becomes active, the edema will decrease (case 2 in Kaplan's series).[1p]

The most prominent manifestations are edema, prominence of superficial veins, cyanosis, palpable venous cord, coolness of the involved side, tenderness over the involved vein, fulness over the anterior region of the chest and shoulder and rubrocyanosis.

The blood pressure may be elevated on the involved side, the venous pressure increased, the circulation time retarded, the oxygen saturation of blood decreased and the temperature of the skin lowered.

Since the initial manifestations are secondary to vasospasm, treatment should be directed toward removing this element. Stellate sympathetic ganglion block with 10 cc. of 0.5 per cent procaine hydrochloride done by the anterior route seems to be the most direct attack on this factor. Elevation will control the edema in the early stages and compression in the later stages. Foci of infections should be eliminated and search made for primary causes of venous stasis and increased coagulability of the blood. In the present series the thrombus was most frequently in the subclavian vein rather than in the axillary vein. Despite energetic treatment, the late results have proved disappointing, with residual effects present in over 75 per cent of the reviewed cases. This emphasizes the need of early adequate treatment of this form of thrombosis with regional sympathetic ganglion block and elevation of the extremity followed by the use of compression bandages and gradual resumption of activity within the limitations of the recurrence of symptoms, particularly edema, which, if allowed to persist, will result in permanent incapacitation.

## SUMMARY

A review of 16 personal cases of "effort" thrombosis of the axillary and subclavian veins and of 56 cases collected from the literature is presented.

# EFFECTS AND FATE OF BLOOD TRANSFUSIONS IN NORMAL DOGS

RAY SEAVERS, M.D.
AND
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IN MANY types of shock the use of blood transfusions is a time-honored method of attempting to correct the presumed disparity between the volume of circulating blood and the capacity of the vascular bed. Although considerable work has been done studying the effects of blood transfusions and other intravenously administered fluids in the treatment of shock, there is an incomplete understanding of what happens when a blood transfusion is given to a normal person or animal.

Boycott and Oakley [1] stated that after a transfusion of whole blood in dogs the plasma volume returns to normal in two to three days and the blood volume is increased for at least two days in proportion to the volume of red cells added. They also reported that the injected protein disappears from the blood stream within the same period. Krumbhaar and Chanutin [2] have reported similar results. According to Sibley and Lundy,[3] twenty-four hours after a blood transfusion in human beings the changes which occur in the blood represent only the effect of the addition of the red cells. Numerous workers have studied the effects of plasma transfusions in both normal patients and animals.

Since a blood transfusion is often given in anticipation of a shocking operation or as an emergency measure in the treatment of "shock" and since relatively little information is available in the literature concerning the immediate effects of transfusions in normal persons, it is felt that the present study may serve as a basis of a clearer understanding of the results which may be expected from blood transfusions during the time of administration and immediately thereafter.

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From the Department of Surgery, University of Utah Medical School.

Aided by a grant for the study of surgical shock from the United States Public Health Service. (Grant No. RG-115.)

1. Boycott, A. E., and Oakley, C. L.: The Adjustment of Blood Volume after Transfusion, J. Path. & Bact. **38**:91, 1934.

2. Krumbhaar, E. B., and Chanutin, A.: Studies in Experimental Plethora in Dogs and Rabbits, J. Exper. Med. **35**:847, 1935.

3. Sibley, H. L., and Lundy, L. S.: The Blood Volume and Hemoglobin after Transfusion, Surg., Gynec. & Obst. **67**:490, 1938.

## METHOD AND CALCULATIONS

Donor blood, obtained under sterile conditions from normal healthy dogs, was citrated by adding 10 cc. of 2.5 per cent sodium citrate in isotonic sodium chloride solution to each 90 cc. of blood. In all the experiments here reported, transfusions consisted of freshly drawn, matched blood.

Recipient dogs were anesthetized lightly with 5 per cent pentobarbital sodium solution intravenously and prepared for the experiment by intubating the trachea, cannulating the carotid artery, exposing the femoral vein and catheterizing the bladder. Operative procedures were performed aseptically.

The following methods and calculations were employed:

*Hemoglobin Content.*—The photoelectric method as described by Evelyn and Mallory [4] was used.

*Hematocrit Value.*—This was measured in Wintrobe tubes centrifuged for 15 minutes at 3,000 revolutions per minute.

*Protein Concentration.*—The falling drop method of Barbour and Hamilton [5] was used. The specific apparatus and technic were checked against the micro-Kjeldahl and Biruet methods using a standard albumin solution.

*Plasma Volume and Blood Volume.*—These were determined by the dye method (T-1824)—Price and Longmire's modification of the Gibson and Evelyn technic.[6]

*Total Hemoglobin Mass, Circulating Cell Volume, Red Cell Size and Total Protein Mass.*—These were calculated as described by Price and his associates [7] and Metcalf.[8]

*Blood Pressure.*—A mercury manometer was attached to the carotid cannula and the mean arterial pressure recorded continuously on a kymograph.

*Nonprotein Nitrogen.*—The usual method of Folin and Wu adapted to the photoelectric colorimeter [9] was used.

*Respiratory Rate, Respiratory Volume and Oxygen Uptake.*—These were recorded and measured by means of a Sanborn "metabolism tester."

*Cardiac Output.*—This was determined by the direct application of the Fick principle.

*Arterial and Venous Oxygen Content.*—These were determined by Peter's and Van Slyke's method using a manometer Van Slyke apparatus.[10]

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4. Evelyn, K. A., and Mallory, H. T.: Micro-Method for the Determination of Oxyhemoglobin, Methemoglobin and Sulfhemoglobin, in a Single Sample of Blood, J. Biol. Chem. **126**:655, 1938.

5. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625, 1946.

6. Price, P. B., and Longmire, W. P.: The Use of T-1824 in Plasma Volume Determinations, Bull. Johns Hopkins Hosp. **71**:51, 1942.

7. Price, P. B.; Hanlon, C. R.; Longmire, W. P., and Metcalf, W.: Experimental Shock: I. Effects of Acute Hemorrhage in Healthy Dogs, Bull. Johns Hopkins Hosp. **69**:327, 1941.

8. Metcalf, W.: The Fate and Effects of Transfused Serum or Plasma in Normal Dogs, J. Clin. Invest. **23**:403, 1944.

9. Notes on Operation of Evelyn Photoelectric Colorimeter, Philadelphia, Rubicon, 1939.

10. Peters, J. P., and Van Slyke, G. D.: Qualitative Clinical Chemistry, Baltimore, (Williams & Wilkins Company), 1932.

*Statistical Analysis.*—The experimental data were analyzed statistically by computing the standard error of all the means and testing the significance of the standard error of the difference between means when it was desired to show the significance of a curve.

## RESULTS

The following experiments were carried out on healthy anesthetized dogs to determine:

A. Effects of anesthesia on controls.

1. No water given, 9 animals.
2. Water given by stomach tube, 3 animals. Isotonic sodium chloride solution given by vein, 1 animal.

TABLE 1.—*Summary of Results of Control Experiments Showing Mean Values*

| | Hours | | | | | No. of Experiments |
|---|---|---|---|---|---|---|
| | 0 | 2 | 4 | 6 | 8 | |
| Hemoglobin (Gm./100 cc.) | 14.4 ± 0.3 | 15.2 | 16.0 | 16.2 | 16.7 ± 0.8* | 9 |
| Hematocrit value | 42.3 ± 1.4 | 44.8 | 45.9 | 48.1 | 49.6 ± 1.7* | 9 |
| Protein concentration (Gm./100 cc.) | 7.25 ± 0.21 | 7.22 | 7.33 | 7.42 | 7.60 ± 0.22* | 9 |
| Plasma volume (cc./Kg.) | 50.3 ± 1.8 | 48.5 | 54.8 | 42.3 | 40.4 ± 1.4* | 9 |
| Blood volume (cc./Kg.) | 80.9 ± 2.9 | 84.0 | 78.2 | 75.2 | 73.6 ± 1.3* | 9 |
| Total circulating hemoglobin (Gm./Kg.) | 11.82 ± 0.59 | 12.50 | 12.50 | 12.30 | 12.45 ± 0.60 | 9 |
| Total circulating protein (Gm./Kg.) | 3.58 ± 0.31 | 3.49 | 3.28 | 3.28 | 3.01 ± 0.09* | 9 |
| Circulating cell volume † (cc./Kg.) | 31.3 | 33.7 | 33.3 | 33.2 | 33.7 ± ... | 9 |
| Temperature | 100.9 ± 0.4 | 98.5 | 100.5 | 100.5 | 102.5 ± 6.0 | 9 |
| Pulse | 180.0 ± 4.5 | 173.0 | 173.0 | 182.0 | 177.0 ± 4.8 | 9 |
| Respiratory rate | 15.3 ± 3.3 | 19.7 | 21.2 | 19.7 | 19.0 ± 2.0 | 9 |
| Blood pressure | 150.0 ± 4.0 | 149.0 | 153.0 | 156.0 | 148.0 ± 18.0 | 9 |
| Weight (Kg.) | 20.0 ± 1.5 | .... | .... | .... | ..... | 9 |

* Represents a significant difference between this mean and the initial mean.
† Circulating cell volume.

B. Effects of transfusion.

1. No water given, 15 animals.
2. Water given by stomach tube, 3 animals.

*A. 1. Effects of Anesthesia Without Hydration on Controls.*—Nine dogs were anesthetized, and the previously described measurements were made over a period of eight hours. Table 1 summarizes the results. It will be seen that significant changes were observed in the hemoglobin, hematocrit level, plasma volume, blood volume, protein concentration, total hemoglobin mass, circulating cell volume and total circulating protein mass but that no significant changes were noted in the pulse, temperature, respiratory rate or blood pressure.

Figure 1 *A* represents graphically the changes in hematocrit level, blood volume and plasma volume in healthy anesthetized dogs over a period of eight hours. At the end of eight hours the increase in hematocrit value was 7.3 mm., or 15 per cent. The values obtained for hemoglobin concentration closely paralleled those for the hematocrit value. The plasma volume had decreased 19 per cent below its basal level by eight hours and the blood volume decreased 9.5 per cent. The reciprocal relationship of hematocrit value to plasma volume is well illustrated.

Figure 1 *B* represents changes in protein concentration, total circulating protein mass and total hemoglobin mass. Protein concentration

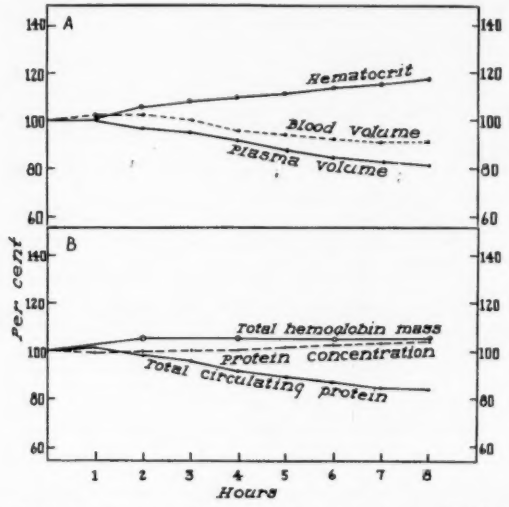


Fig. 1.—Control study. *A*, effects of eight hours of pentobarbital anesthesia and withholding water on hematocrit, blood volume and plasma volume of normal dogs. *B*, effects of eight hours of pentobarbital anesthesia and withholding water on total hemoglobin mass, protein concentration and total circulating protein mass of normal dogs.

gradually increased to 5 per cent above normal. The total circulating protein mass, however, decreased to 16 per cent below the original value, a disappearance rate of 2.9 per cent of the total per hour. By the end of two hours the total hemoglobin mass had increased 5 per cent. This increase was maintained until the end of the experiment. The circulating cell volume showed a curve similar to that of the total hemoglobin mass. There was no appreciable alteration in the mean size of individual red blood cells.

*A. 2. Effects of Anesthesia Plus Hydration on Controls.*—An entirely different set of values was obtained when the animals were kept hydrated during the eight hour period of anesthesia. The procedure just described was repeated in 3 dogs except that water was administered through a stomach tube at the rate of 3 cc. per kilogram per hour.

Although this series is small, it is evident that there was no pronounced tendency for plasma volume, blood volume or total circulating protein mass to decrease below the normal. Nor was there a significant increase of hematocrit value, hemoglobin or protein concentration.

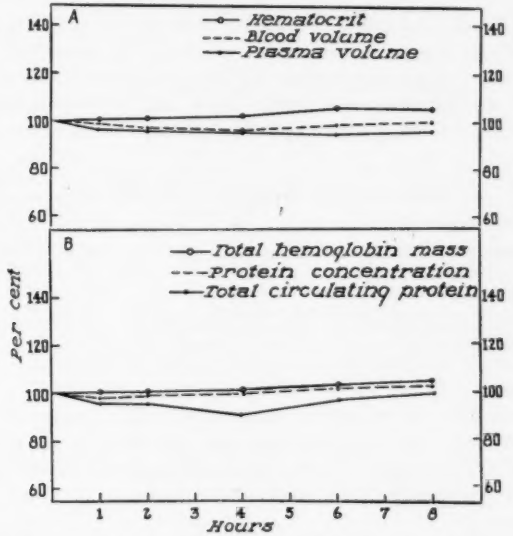


Fig. 2.—Control study. *A*, effects of eight hours of pentobarbital anesthesia and the administration of water through a stomach tube on the hematocrit, blood volume and plasma volume of a normal dog. *B*, effects of eight hours of pentobarbital anesthesia and the administration of water through a stomach tube on total hemoglobin mass, protein concentration and total circulating protein mass of a normal dog.

Figure 2 *A* shows the changes in hematocrit value, blood volume and plasma volume in a typical experiment. The increase in the hematocrit value was relatively slight and was probably due to increased total hemoglobin mass. Plasma volume and blood volume showed no significant alteration at the end of eight hours. During the experiment there were, however, minor fluctuations of the plasma volume amounting to as much as 5 per cent of the initial value.

Figure 2 *B* shows changes in protein concentration, total circulating protein mass and total hemoglobin mass. These values also remained relatively stable during the eight hour period.

In 1 experiment isotonic sodium chloride solution was given continuously by vein at the rate of 3 cc. per kilogram per hour. The results obtained were the same as when the water was given by stomach tube.

A comparison of figure 2 with the first figure demonstrates the effect of the administration of water. When water is given, all the measurements tend to remain relatively stable and the pronounced effects apparently due to dehydration do not occur.

*B. 1. Effects of a Blood Transfusion Without Supplementary Hydration.*—Fifteen dogs were used in this series, and the procedure employed was the same as for the controls except that a transfusion was given. Eight of the animals were intact, and 7 were splenectomized. The splenectomized animals were used in an attempt to eliminate the factor

TABLE 2.—*Values of the Citrated Blood Used for the 15 Transfusions*

| | |
|---|---|
| Average hemoglobin | 13.3 ± 0.7 Gm./100 cc. |
| Average hematocrit | 38.0 ± 1.5 mm. |
| Average protein concentration | 7.02 ± 0.17 Gm./100 cc. |
| Average amount of blood in each transfusion | 275.0 ± 17.0 cc. |
| Average amount of plasma in each transfusion | 158.0 ± 11.0 cc. |
| Average amount of plasma protein in each transfusion | 12.3 ± 0.7 grams |
| Average amount of hemoglobin in each transfusion | 34.4 ± 2.8 grams |

of the expansile canine spleen, which occasionally caused considerable change in blood volume during the first two hours of an experiment. No significant differences between splenectomized and nonsplenectomized animals were observed, however; so all have been included in the following summary.

Average values for the fifteen transfusions are given in table 2.

Table 3 gives in summarized form mean values obtained in this series of experiments. The basal period prior to the transfusion averaged two hours, and on the average sixty minutes was required to inject the blood. The third column of figures represents values obtained twenty minutes after cessation of the transfusion. In every case the effects of the transfusion were followed for five hours after its termination. For the sake of comparison, the values obtained from the series of control experiments are included in figures 6, 7 and 8. The period of the blood transfusion is indicated by a solid bar in the upper left hand section of each figure.

Figure 3 shows the changes in hematocrit value and protein concentration. As is evident, after transfusion both valves increased at fairly

regular rates. In each case the value obtained at eight hours was equal to the percentage value of the control plus the percentage value of hemoglobin or protein added. Since the changes in the hemoglobin level paralleled those of the hematocrit reading, they are not shown.

Figure 4 represents changes in plasma volume and urinary output following transfusion. It will be seen that two hours after transfusion the plasma volume had returned to the pretransfusion level and five

TABLE 3.—*Summary of the Transfusion Experiments, Showing Mean Values*

| | Hours | | | | | | | No. of Experiments |
|---|---|---|---|---|---|---|---|---|
| | 0 | 2 | 3½ | 4 | 5 | 7 | 8 | |
| Hemoglobin (Gm./100 cc.) | 15.9 ± 0.5 | 16.5 | 17.2 | 18.0 | 18.4 | 18.8 | 18.9 ± 0.4* | 15 |
| Hematocrit value (mm.) | 48.7 ± 1.5 | 50.1 | 53.8 | 55.5 | 56.5 | 57.7 | 58.0 ± 1.1* | 15 |
| Protein concentration (Gm./100 cc.) | 7.05 ± 0.12 | 6.96 | 7.18 | 7.28 | 7.54 | 7.57 | 7.57 ± 0.14* | 15 |
| Plasma volume (cc./Kg.) | 46.9 ± 1.2 | 47.0 | 53.9 ± 2.0* | 51.6 | 46.6 | 41.5 | 40.1 ± 1.4* | 15 |
| Blood volume (Gm./Kg.) | 85.6 ± 1.9 | 88.0 | 106.0 ± 3.0* | 101.0 | 97.5 | 89.0 | 83.9 ± 3.0 | 15 |
| Total circulating hemoglobin (Gm./Kg.) | 13.4 ± 0.6 | 14.3 | 18.8 ± 0.7* | 18.1 | 17.5 | 16.4 | 15.6 ± 0.6* | 15 |
| Total circulating protein (Gm./Kg.) | 3.30 ± 0.09 | 3.30 | 3.78 ± 0.15* | 3.68 | 3.41 | 3.07 | 2.98 ± 0.03* | 15 |
| Circulating cell volume (cc./Kg.) | 37.6 | 39.8 | 52.0 | 52.9 | 49.9 | 46.5 | 45.5 | 15 |
| Temperature | 100.2 ± 0.3 | 100.8 | 101.0 | 101.3 | 101.8 | 102.8 | 102.0 ± 0.7* | 15 |
| Pulse | 146.0 ± 7.0 | 152.0 | 152.0 | 150.0 | 146.0 | 153.0 | 158.0 ± 7.0* | 15 |
| Respiratory rate | 11.5 ± 5.1 | 13.5 | 15.5 | 14.5 | 15.0 | 20.8 | 22.5 ± 5.1* | 13 |
| Respiratory volume (cc./Kg./min.) | 157.0 ± 25.0 | 198.0 | 194.0 | 190.0 | 205.0 | 236.0 | 258.0 ± 23.0* | 10 |
| Oxygen uptake (cc./Kg./min.) | 7.0 ± 0.6 | 7.6 | 7.7 | 7.8 | 8.2 | 8.6 | 8.6 ± 0.6 | 10 |
| Blood pressure (mm. Hg.) | 145.0 ± 3.0 | 144.0 | 151.0 | 148.0 | 148.0 | 141.0 | 140.0 ± 4.0 | 10 |
| Nonprotein nitrogen (mg./100 cc.) | 34.2 | ..... | ..... | 33.2 | 32.2 | 31.7 | ..... | 3 |
| Weight (Kg.) | 14.9 ± 1.2 | ..... | ..... | .... | .... | .... | ..... | 15 |
| Urinary output (cc./hr.) | 12.8 ± 1.1 | 12.8 | 27.8* | 50.5 | 20.4* | 13.0 | 12.0 ± 1.3 | 10 |

* Represents a significant difference between this mean and the initial mean.

hours after transfusion the plasma volume had decreased to 14 per cent below normal. This is a significant drop below normal; it is also a significant increase above what occurred in the control dogs at the same period. The urinary output was doubled during the hour of the transfusions and was increased fourfold for an hour after. The output returned to normal two hours after the transfusion.

The blood volume (fig. 5 *A*) returned to normal at the end of five hours; however, it was significantly increased above the blood volume obtained in the control series.

The total circulating hemoglobin mass showed an immediate increase of 40 per cent, which indicated a pronounced influx of red cells into the circulation over and above the injected donor cells. The total circulating hemoglobin mass then steadily decreased, until at the end of five

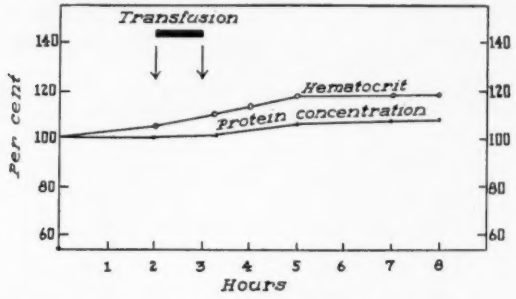


Fig. 3.—Effects of transfusions on hematocrit and protein concentration of healthy dogs anesthetized with pentobarbital. No water was given.

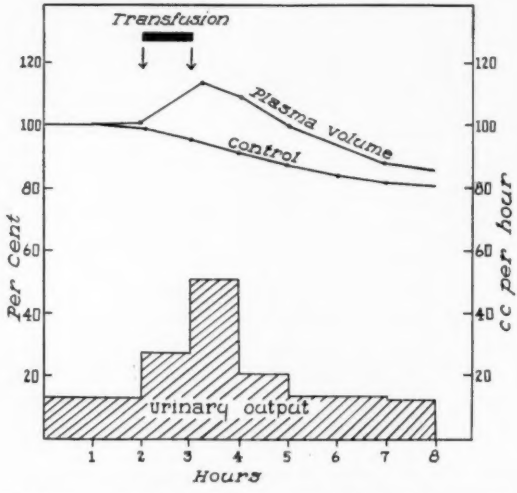


Fig. 4.—Effects of transfusions on plasma volume and urinary output of healthy dogs anesthetized with pentobarbital. No water was given.

hours the increase represented only the amount of injected red blood cells. The circulating cell volume showed a similar curve. No change was observable in the average size of red blood cells after the transfusion.

An interesting observation is that after the transfusion the total circulating protein mass gradually decreased. As shown in figure 5 *B*, after the initial increase following transfusion, the total circulating protein mass gradually diminished at such a rate that three hours after the transfusion an amount of protein equivalent to that injected had disappeared. At the end of five hours the total protein mass was 9 per cent below the pretransfusion level. This is a significant reduction; it is also a significant increase above what was obtained in the control experiments although the total amount of protein disappearing from the circulation after transfusion (1.32 Gm. per kilogram) was significantly

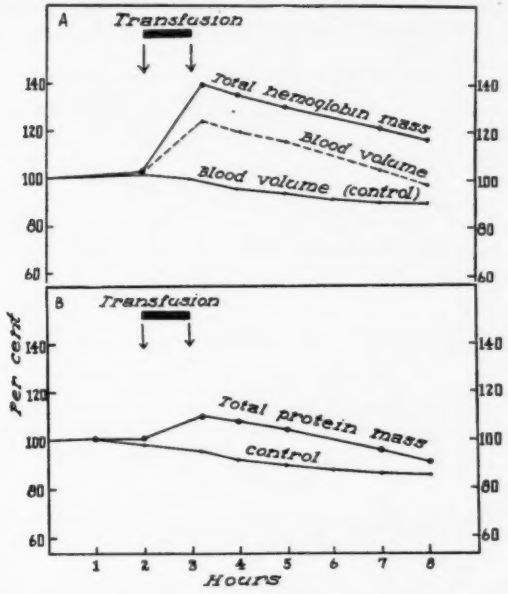


Fig. 5.—*A*, effects of transfusions on total hemoglobin mass and blood volume of healthy dogs anesthetized with pentobarbital. No water was given. *B*, effects of transfusions on total circulating protein mass of healthy dogs anesthetized with pentobarbital. No water was given.

greater than the amount (0.48 Gm. per kilogram) disappearing in the same length of time in the controls.

Significant increases were observed in temperature, respiratory rate and respiratory volume (fig. 6). It should be noted, however, that no effort was made to control the temperature of the dogs in the transfusion series, whereas in the series of control experiments which were performed in midsummer the dogs' temperature was controlled by

means of wet towels and an electric fan. Increase in oxygen consumption following transfusion was not significant. There was no significant change in blood pressure or pulse rate following the transfusion.

Plasma nonprotein nitrogen concentration was followed in 3 animals. No increase was noted after transfusion; on the contrary, an average fall of 8 per cent was observed four hours later.

No conclusive evidence could be obtained in 3 dogs indicating either increase or decrease in the cardiac output following transfusion.

*B. 2. Effect of a Blood Transfusion Plus Supplementary Hydration.*—In an effort to reproduce the clinical problem in which many patients have an opportunity to drink water during the pretransfusion and post-transfusion period, 3 animals were given transfusions but, as in

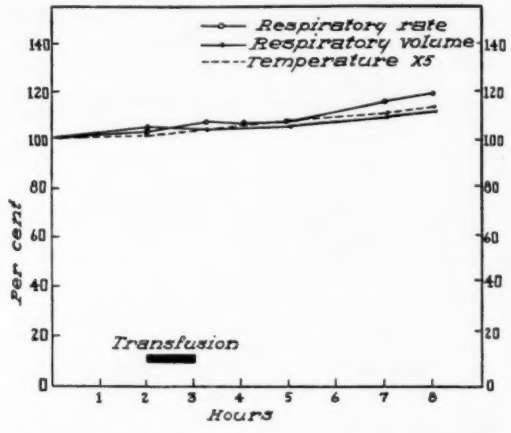


Fig. 6.—Effects of transfusion on respiratory rate, temperature and respiratory volume of healthy dogs anesthetized with pentobarbital. No water was given.

the case of the extra control dogs, they were given water through a stomach tube. Here again the results were different.

During the first two hours before transfusion, plasma volume and blood volume increased slightly. After transfusion the abrupt rise in plasma volume and blood volume was noted. This was followed by a rapid decline (fig. 7). The plasma volume returned to within 2 per cent of normal six hours after the transfusion but not below normal as was the case with the dogs which were not kept hydrated. The blood volume six hours after transfusion was still increased in excess of the mass of injected red cells. The hematocrit value (fig. 8) showed the usual increase immediately after transfusion, but then a leveling off was seen rather than a tendency to increase further. The urinary output increased

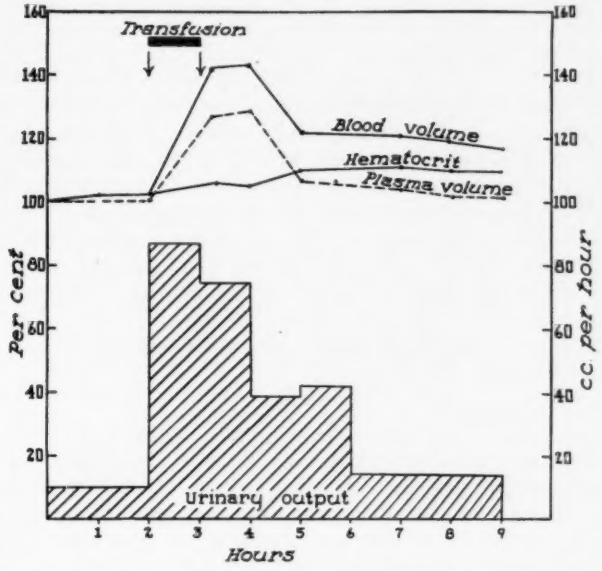


Fig. 7.—Effects of transfusion on blood volume, hematocrit, plasma volume and urinary output of a normal dog. Water was given through a stomach tube during the experiment.

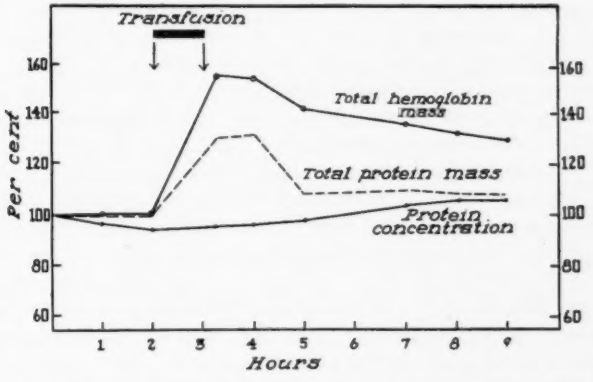


Fig. 8.—Effects of a transfusion on total hemoglobin mass, total protein mass and protein concentration of a healthy dog. Water was given through a stomach tube during the experiment.

eightfold during the transfusion and was increased sevenfold for the first hour thereafter. In the second and third hours after transfusion the output was four times normal, and then it returned to the normal range.

After the immediate increase following the transfusion the total protein mass (fig. 8) decreased rapidly and then leveled off at a value 8 per cent above normal. There was no tendency for the total mass of protein to fall below the pretransfusion level. The protein concentration showed a drop before transfusion and a gradual increase after the transfusion to 6 per cent above normal. The total hemoglobin mass increased rapidly to 55 per cent above normal, an increase of 40 per cent above that expected. It then decreased, until six hours after the transfusion it was 30 per cent above normal, an increase of 15 per cent above that expected.

There was no appreciable alteration of respiratory rate, temperature or blood pressure.

## COMMENT

When normal healthy dogs are subjected to eight or nine hours of anesthesia, pronounced changes occur. Plasma volume, blood volume and total protein mass decrease below normal; the hematocrit value, hemoglobin, protein concentration and total hemoglobin mass increase (fig. 1). Except for the rise in total hemoglobin mass, these changes can be prevented by keeping the animal hydrated. Obviously the dehydration which occurs in animals during anesthesia is considerable and can produce significant changes in most of the values being studied here. The effects of transfusion in these experiments must be measured in relation to the base line of the effects of dehydration alone.

The most important change in the cellular elements of the blood following a transfusion occurred in the total circulating hemoglobin mass. Presumably the transfusion served as some type of impetus for erythrocyte depots to discharge their stores into the circulation, since immediately after the transfusion the total hemoglobin mass increased out of proportion to the amount of foreign red cells added. After this pronounced increase, the total hemoglobin mass gradually decreased to the expected value. As this occurred in splenectomized dogs as well as in nonsplenectomized dogs, it would appear that there is either a "reservoir" of red blood cells other than the spleen or the initial method of calculation failed to include cells which were made available after the transfusion. Although the spleen does serve as a sizable "reservoir" of red blood cells in the dog, evidence has been brought forward [11] which seems to show that "stores" of this nature do not occur in man.

11. Ebert, R. V., and Stead, E. A.: Demonstration That in Normal Man No Reserves of Blood Are Mobilized by Exercise, Epinephrine and Hemorrhage, Am. J. M. Sc. **201**:655, 1941.

It is to be expected that the fate of the injected cells is ultimately that of disintegration. Callender [12] has shown that in man the curve of destruction of transfused red blood cells is linear and that the average life is sixty days. This may be true of injected cells in dogs.

The plasma volume is not increased quantitatively for any length of time by the addition of the plasma in blood. As early as twenty minutes after the transfusion some of the fluid disappeared, and two hours later the plasma volume had returned to normal. Even in hydrated dogs (fig. 7) the plasma volume rapidly returned to normal. This initial translocation of fluid is rapid and is apparently an attempt on the part of the body mechanism to restore the plasma volume to a normal level. Since the excess urinary output accounted for one third of the lost fluid in the nonhydrated dogs and all the fluid lost in the hydrated dogs it is thought that this may be one of the main mechanisms for adjusting the plasma volume when it is increased by a transfusion.

Because of the influx of red cells into the blood stream the blood volume immediately after the transfusion was increased out of proportion to the amount of blood added. By the end of five hours, however, the blood volume decreased (because of decreasing plasma volume and total hemoglobin mass) until it was above the control only by the volume of the red blood cells added. This was demonstrated in the nonhydrated dogs. Why the total hemoglobin mass should remain increased above the expected value in hydrated dogs is difficult to explain.

The effect and fate of the injected protein is an intriguing problem. After transfusion the injected protein or its equivalent was rapidly removed from the blood stream. This occurred in the hydrated dogs as well as the nonhydrated dogs. In accord with Whipple's concept of a dynamic equilibrium between plasma protein and tissue protein, it is conceivable that this temporary excess of plasma protein is adjusted either by an increased rate of removal from the blood stream or by a decreased amount of plasma protein entering the blood stream, the rate of removal remaining constant. Although the fate of the injected protein is unknown, there are several possibilities: The protein may be catabolized; it may be partially broken down into large aggregates of amino acids and be resynthesized, or it may be stored as plasma protein. Howland and Harkins,[13] working with phlorhizinized dogs, have shown that injected plasma protein is not metabolized to amino acids before being utilized, as no excess nitrogen or sugar is found

12. Callender, S. T.; Powell, E. O., and Witts, L. J.: Life-Span of Red Cells in Man, J. Path. & Bact. **57**:129, 1945.

13. Howland, J. W., and Hawkins, W. B.: Protein Metabolism, Protein Interchange and Utilization in Phlorizinized Dogs, J. Biol. Chem. **123**:99, 1938.

in the urine. That conclusion is corroborated in the present series of experiments by the failure of the plasma nonprotein nitrogen concentration to increase after transfusion.

Since there is fairly good evidence for the existence of limited plasma protein stores [14] and most certainly for fairly large stores of plasma protein–building material,[15] it is possible that some of the excess protein enters those stores. Possibly the majority of the protein is broken down and resynthesized where needed. Some of the plasma protein may enter directly into plasma protein stores. Further work is being done in an attempt to ascertain the extent to which these stores can be built up by means of blood transfusion.[16]

## SUMMARY

1. The immediate effects and fate of blood transfusions in normal dogs have been studied. The changes have been compared with those occurring in control animals during similar periods.

2. Pentobarital anesthesia for several hours produced significant changes in hematocrit value, hemoglobin, blood volume, plasma volume, protein concentration and total protein mass of normal dogs.

3. These changes were presumably due to dehydration, as they could be prevented by administration of water by stomach tube.

4. A blood transfusion given to nonhydrated dogs did not effectively increase the blood volume for more than five hours, the plasma volume for more than two hours or the total protein mass for more than three hours.

5. A blood transfusion given to hydrated dogs did not effectively increase the total protein mass or the plasma volume for more than two or three hours.

6. Immediately after a blood transfusion in nonhydrated dogs the blood volume was increased out of proportion to the amount of blood added because of an influx of red blood cells from depots into the circulation. After five hours, however, the net increase in blood volume was equivalent to the mass of injected red blood cells.

14. Calvin, D. B.; Decherd, G., and Herrmann, G.: Plasma Protein Shifts During Diuresis, Proc. Soc. Exper. Biol. & Med. **44**:578, 1940. Beatie, J., and Collard, H. B.: Plasma Protein Storage, Brit. M. J. **2**:507, 1942.

15. Madden, S. C., and Whipple, G. H.: Plasma Proteins, Their Service, Production and Utilization, Physiol. Rev. **20**:194, 1940. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Plasma Protein Regeneration Controlled by Diet., J. Exper. Med. **59**:251, 1934.

16. Seavers, R., and Price, P. B.: Effects of Sublethal Hemorrhage in Normal Dogs and in Dogs Previously Transfused with Whole Blood, Surg., Gynec. & Obst. **88**:178-184, 1949.

# SPONTANEOUS RUPTURE OF THE DISEASED SPLEEN

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INTRA-ABDOMINAL hemorrhage, regardless of the cause, remains one of the most important of all the conditions constituting acute surgical emergencies. The ultimate result is the same whether the hemorrhage results from failure of diagnosis or from an error in judgment of the optimum time for operative intervention.

With the exclusion of bleeding of a genital organ in females and bleeding due to trauma, extremely difficult diagnostic problems remain. Included in these, all of which come under the category of "spontaneous intra-abdominal hemorrhage," are (1) rupture of an abdominal aneurysm; (2) rupture of a splanchnic vessel in patients with arteriosclerosis (abdominal apoplexy),[1] and (3) splenic rupture in either a normal or a diseased spleen. It is the latter of these with which this paper is primarily concerned.

Nontraumatic spontaneous rupture of an apparently normal spleen, although rare, is considered by some surgeons as a definite clinical entity. Dahle,[2] in reviewing the literature, found 14 cases and added 1 of his own. In the same year Lundell[3] reviewed 20 previously reported cases and came to the conclusion that a healthy spleen would not rupture spontaneously. Silverman and Randazzo[4] reported 1 proved case in 1946. McCoy[5] reported a case of spontaneous rupture which occurred during sleep.

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1. Cushman, G. F., and Kilgore, A. R.: Syndrome of Mesenteric or Subperitoneal Hemorrhage (Abdominal Apoplexy), Ann. Surg. **114**:672, 1941. Marks, M., and Freedlander, S. O.: Spontaneous Intra-Abdominal Hemorrhage, ibid. **121**:191, 1945.

2. Dahle, M.: Rupture of Normal Spleen Without Known Cause, Acta chir. Scandinav. **75**:519, 1934.

3. Lundell, G.: Spontaneous Rupture of the Spleen, Acta chir. Scandinav. **75**:547, 1934.

4. Silverman, I., and Randazzo, A. P.: Nontraumatic Spontaneous Rupture of the Spleen, Arch. Surg. **53**:355 (Sept.) 1946.

5. McCoy, J. C.: Splenectomy for Rupture of the Spleen: Report of Four Cases, Ann. Surg. **74**:13, 1911.

Spontaneous rupture of a diseased spleen is a definite pathologic entity. Noland and Watson [6] reported 3 cases of rupture occurring in a malarial spleen. Leighton [7] described a similar nontraumatic rupture of the spleen in a patient with malaria. Russ and Gaynor [8] reported a case of ruptured malarial spleen successfully treated by means of splenectomy in 1945. McCarthy and Knoepp [9] have reported 2 cases. In the first the rupture was caused by malaria, in the second it occurred in a patient with infectious mononucleosis and associated splenomegaly and in the third it took place in a patient with multiple hemangiomas involving the spleen. Darley, Black, Smith and Good [10] have reported a similar occurrence in a case of infectious mononucleosis. Thorpe,[11] in a personal communication, described a rupture which resulted from repeated attempts to palpate the spleen in a patient with infectious mononucleosis.

Conner and Downes [12] have reported a spontaneous rupture of the spleen in a case of typhoid. Splenectomy was performed, and the patient recovered. Similar splenic ruptures have been described as occurring in instances of acute leukemia,[13] sarcoidosis [14] and reticulum cell sarcoma with primary involvement of the spleen.[15]

Spontaneous rupture implies that there has been no history of trauma or that the degree of trauma has been so insignificant that it may not be considered as a causative factor. Of the many and varied diseases of the spleen which have led to ultimate spontaneous rupture, human malaria is undoubtedly the one of greatest import. This is especially true during the present period, with the growing reports of relapsing vivax malaria of Pacific origin occurring in veterans.

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6. Noland, L., and Watson, F. C.: Spontaneous Rupture of the Malarial Spleen: Report of Three Cases, Ann. Surg. **57**:72, 1913.

7. Leighton, W. E., cited by Conner and Downes.[12]

8. Russ, S. E., and Gaynor, J. S.: Spontaneous Rupture of a Malarial Spleen, J. A. M. A. **127**:758 (March 31) 1945.

9. McCarthy, A. M., and Knoepp, L. F.: Spontaneous Rupture of the Spleen, Am. J. Surg. **65**:413, 1944.

10. Darley, W.; Black, W. C.; Smith, C., and Good, F. A.: Spontaneous Splenic Rupture in Infectious Mononucleosis: Case and Pathologic Report, Am. J. M. Sc. **208**:381, 1944.

11. Thorpe, H. R.: Personal communication to the author.

12. Conner, L. A., and Downes, W. A.: Spontaneous Rupture of the Spleen in Typhoid Fever with Report of a Case Cured by Operation, Am. J. M. Sc. **147**:332, 1914.

13. Rubnitz, A. S.: Spontaneous Rupture of the Spleen Due to Acute Leucemia or Acute Leucemia Due to Trauma of Spleen . . . Which? Report of Case and Review of Literature, J. Lab. & Clin. Med. **28**:972, 1943.

14. James, I., and Wilson, A. J.: Spontaneous Rupture of the Spleen in Sarcoidosis, Brit. J. Surg. **33**:280, 1946.

15. Littlefield, J. B.: Spontaneous Rupture of the Spleen: Report of Three Cases, Surg., Gynec. & Obst. **82**:207, 1946.

Splenic rupture is as great a danger in patients with therapeutic malaria as in patients with acquired malaria. Bachmann [16] reported a case which occurred twenty-five days after the injection of 5 cc. of blood containing the plasmodia of tertian malaria, sudden death occurring during the second paroxysm. Twitchell [17] described a similar case in which rupture occurred after the patient had his eighteenth paroxysm of fever. The diagnosis was made by exploratory laparotomy; however, the spleen was not removed in view of the patient's poor condition. Postmortem examination confirmed the diagnosis.

It is generally conceded that there are two mechanisms which might be the cause of spontaneous rupture of a malarial spleen. The first, and least important, consists of a tear occurring in one of the fissures or through the parenchymal substance of the spleen without subcapsular hemorrhage. The second, and more frequent, consists of the formation of a subcapsular hematoma which ultimately ruptures. On consideration of the facts regarding the pathologic patterns followed by human malaria,[18] the events in either type become more apparent.

Malarial parasites, after entrance and dissemination throughout the body, tend to become localized predominantly in the organs possessing blood sinuses.[19] The most prominent of these is the spleen, which undergoes marked hypertrophy and hyperplasia. The splenic corpuscles show striking proliferative reactions. The lymphoid structures undergo toxic necrosis and grave depletion. Embolic occlusions of capillaries and arterioles result in punctate hemorrhages and toxic and necrotizing lesions throughout the spleen. The consequent boggy splenic pulp with its increased fragility in an already greatly enlarged spleen predisposes to spontaneous rupture of the first type. When a large vessel is involved, splenic infarction and/or hemorrhage may be sufficient to form a large subcapsular hematoma. The resultant disproportion between the size of the spleen and the resistance of the capsule predisposes to rupture of the second type.

The diagnosis should be suspected when the patient complains of spontaneous pain in the left side of the abdomen, followed by symptoms of peritoneal and/or diaphragmatic irritation coupled with

16. Bachmann, F.: Spontaneous Rupture of the Spleen in Therapeutic Malaria, München. med. Wchnschr. **73**:528, 1926.

17. Twitchell, E. W.: Spontaneous Rupture of Spleen Following Malaria Therapy for General Paresis, California & West. Med. **33**:512, 1930.

18. Cannon, P. R.: Some Pathologic Aspects of Malaria, in a Symposium on Human Malaria, no. 15, American Association for the Advancement of Science, 1941.

19. Cannon, P. R.; Sullivan, F. L., and Neckermann, E. F.: Conditions Influencing the Disappearance of Living Bacteria from the Blood Stream, J. Exper. Med. **55**:121, 1932.

a clinical picture of hemorrhagic shock, and gives either a definite history of malaria, acquired or induced, with recent or recurrent relapses manifested by the usual paroxysm or a history of attacks of unexplained fever, accompanied with chills, headache and malaise following return from endemic areas. A definite diagnosis of malaria is difficult to make when the latter history is given. This is especially true in persons who have taken prophylactic antimalarial therapy during their stay in an endemic area and have discontinued it when they returned to their homes. For example, the patient in the accompanying case report had always assumed that his symptoms, which had manifested themselves after his return from the South Pacific, were due to malaria, but a definite diagnosis had never been made.

The physical findings parallel those in cases of ruptured spleen from any cause. These include signs of hemorrhage (low blood pressure, fast pulse, weakness, pallor, air hunger and restlessness); abdominal tenderness and rigidity, which may be generalized but is most pronounced in the left upper quadrant; rebound tenderness, with referral of pain to the left upper quadrant and/or the left shoulder; increased splenic dulness; a fluid wave, and Ballance's sign, or fixed dulness in the left flank due to the enlarging hematoma and shifting dulness in the right flank due to unclotted blood and serum.

Blood studies have proved of value. Demonstration of the malarial parasite in smears of the peripheral blood or of increasing hemorrhagic anemia, with a falling red blood cell count and hematocrit value, is most helpful. Leukocytosis may or may not be present.

The roentgenographic aids in the diagnosis of spontaneous rupture of the spleen are most important. Webb [20] reported an increased density in the left upper quadrant of the abdomen, elevation of the left side of the diaphragm, displacement of the stomach to the right and free fluid between loops of intestine. Zabinski and Harkins [21] described medial displacement of the colon. Solis-Cohen and Levine [22] and O'Neill and Rousseau [23] have described obliteration of the splenic shadow and a dilatation of the stomach with serrations of the greater

20. Webb, in discussion on Foster, I. M., and Prey, D.: Rupture of Spleen: Analysis of Twenty Cases, Am. J. Surg. **47**:487, 1940.

21. Zabinski, E. J., and Harkins, H. N.: Delayed Splenic Rupture: A Clinical Syndrome Following Trauma, Arch. Surg. **46**:186, 1943.

22. Solis-Cohen, L., and Levine, S.: Roentgen Diagnosis of Lacerated Spleen, Radiology **39**:707, 1942. Levine, S., and Solis-Cohen, Survey Film Diagnosis of Rupture of Acute Surgical Abdomen, Surg., Gynec. & Obst. **78**:76, 1944.

23. O'Neill, J. F., and Rousseau, J. P.: Roentgenologic Examination of the Abdomen As an Aid in the Early Diagnosis of Splenic Injury, Ann. Surg. **121**:111, 1945.

curvature. These findings were present in the accompanying case reported and are well illustrated in the preoperative roentgenograms (fig. 1).

There is no question in regard to treatment. There is bleeding into the peritoneal cavity, and this hemorrhage must be controlled as quickly as possible. The only satisfactory method of accomplishing this is by splenectomy. The amount of blood lost in these cases may be staggering; therefore, adequate shock therapy is the most essential preoperative procedure. Whole blood is the replacement fluid of choice.[24] A muscle-splitting left rectus incision with a T-shaped extension into the left flank is preferred. The spleen is removed most easily by the technic first described by Balfour.[25] Dunphy[26] has recently published an excellent review of Balfour's basic contributions to this field.

## REPORT OF A CASE

R. W., a 36 year old white soldier, a cook, was admitted to Fort Ord Regional-Station Hospital on Aug. 30, 1947. The chief complaint at the time of admission was severe pain in the left shoulder and left upper region of the abdomen of about seventeen hours' duration.

The patient had taken a nap the afternoon of the day before entry. Other than feeling extremely tired, which he attributed to recent long hours of work, he had no complaints. At approximately 4 o'clock he was awakened with a sudden excruciating pain in the left upper region of the abdomen and the left shoulder. During the interim, the pain persisted and became worse. The usual household remedies had been tried, with no results. The only relief was obtained by lying still in one position for long periods. Although he felt extremely tired, he could not sleep. Weakness of a notable degree gradually appeared. The abdominal pain spread to involve all four quadrants. A review of the systems revealed nothing remarkable. There had been no associated nausea or vomiting. The last bowel movement, the evening before admission, had been normal in character. The cardiorespiratory and genito-urinary systems were normal. No history of recent trauma of any kind could be elicited. The patient offered the history of unexplained fever accompanied with chills, headache and malaise of three weeks' duration. He also recalled intermittent sharp twinges of pain, of varying degrees of intensity, located in the left shoulder. The first of these had occurred two weeks prior to his entry to the hospital.

He reported to sick call at his dispensary at 8 a.m. on Aug. 30, 1947, where a diagnosis of spreading peritonitis secondary to a ruptured peptic ulcer was made. The hospital admitting officer obtained a surgical consultation with me immediately after the patient arrived at the receiving and disposition office.

The past history was not significant in any particular except for a story suggestive of recurrent attacks of relapsing malaria. During his service in New Guinea (1943) he had suffered several attacks of illness, primarily chills

24. Dunphy, J. E.: Shock: A Consideration of Its Nature and Treatment, Brit. J. Surg. **32**:66, 1944.

25. Balfour, D. C.: Splenectomy, Surg., Gynec. & Obst. **23**:1, 1916.

26. Dunphy, J. E.: Splenectomy for Trauma; Practical Points in Surgical Technic, Am. J. Surg. **71**:450, 1946.

and fever. He had not reported to sick call during any of these attacks. By comparing his symtoms with those manifested by other soldiers, he made a diagnosis of malaria and treated the disease by self medication (quinacrine hydrochloride [atabrine di-hydrochloride®], dosage not known). Since his return to the United States he had had several similar attacks, and each time he resorted to self treatment. No medication had been taken during the three weeks of illness just prior to his admission. There was no history of previous surgical intervention. The family history was not pertinent.

Physical examination showed the patient to be a spare white man, appearing much older than his actual age of 36 years. He was well developed but appeared to be in only a fair state of nutrition. There was evidence of recent loss of weight. He was extremely apprehensive and restless, tossing from side to side. The face was covered with beads of cold, clammy perspiration. A decided pallor was in evidence. There was no cyanosis. The temperature was 101.8 F. orally. The pulse rate was 100, and it was weak and thready. The respiratory rate varied between 26 and 30. At times a definite air hunger was evident. The examination showed an essentially normal condition except for the chest and abdomen. The left lower intercostal spaces were somewhat narrowed. There was a moderate lag of respiratory excursion of the left thoracic wall. The left side of the diaphragm was elevated on percussion. The pulmonary fields were clear throughout. The cardiac outline was not enlarged. Auscultation revealed a blowing systolic murmur, heard best at the apex. This was thought to be a murmur of the hemic type. The blood pressure was 90 systolic and 50 diastolic. The abdomen was markedly distended. Rigidity and abdominal tenderness were generalized but were most pronounced in the left upper quadrant and left flank. Rebound tenderness was present throughout, with referral of pain to the left upper quadrant and the left shoulder. Shifting dulness was demonstrated in the right flank. A large area of fixed dulness was found in the left flank. No fluid wave could be demonstrated. Auscultation revealed a completely silent abdomen. Rectal examination revealed generalized tenderness in the rectovesical pouch.

The pertinent laboratory findings were as follows: The red blood cell count was 2,200,000. The hemoglobin content was 50 per cent. The hematocrit value was 22. There was slight leukocytosis, with a moderate left shift. Malarial parasites (Plasmodium vivax) were demonstrated in smears of the peripheral blood. The urine was normal. An upright anteroposterior roentgenogram of the chest showed the left leaf of the diaphragm to be elevated (fig. 1). The right leaf was also slightly elevated. An upright scout roentgenogram of the abdomen (fig. 1) showed a large, oval, well circumscribed area of increased density in the left upper quadrant. The gastric air bubble was displaced medially. There were irregular serrations along the greater curvature of the stomach. The slightly distended large bowel was seen occupying a central position in the abdomen. It was surrounded by an area of increased density suggesting intra-abdominal fluid. Free fluid was also suggested by a similar density between the few loops of small bowel visualized and the homogeneous density extending from the extraperitoneal fat along the left gutter.

A diagnosis of intra-abdominal hemorrhage secondary to spontaneous rupture of a malarial spleen was made. Emergency splenectomy was advised.

During the interval before operation, a Levine tube was inserted. The patient received 1 unit of plasma and 1 pint (500 cc.) of whole blood prior to operation.

Laparotomy was accomplished two hours after his admission. After induction of anesthesia with thiopental sodium U. S. P. (pentothal sodium®), plus

curare for relaxation, a woven catheter endotracheal tube was inserted. Anesthesia was maintained by the use of a combination of pentothal sodium,* ether, nitrous oxide, oxygen and curare. The operating table was broken slightly at the level of the costal margin anteriorly and the body rotated slightly to the right and supported in this position by a sand bag in the loin. The abdomen was opened through a long paramedian incision splitting the left rectus muscle, with a T-shaped extension into the left flank. When the peritoneum was opened, a large amount of clotted blood was found in the left upper quadrant extending down into the left gutter. There was a large amount of unclotted blood and serum throughout the remainder of the abdomen. The liver was of normal size and appearance. The immediate field was cleared of bood and the spleen delivered into the wound by advancing the right hand along the free posterolateral aspect of the organ until the upper pole was reached; the spleen was then pushed into the wound. Diaphragmatic adhesions were minimal. The spleen was approximately five times

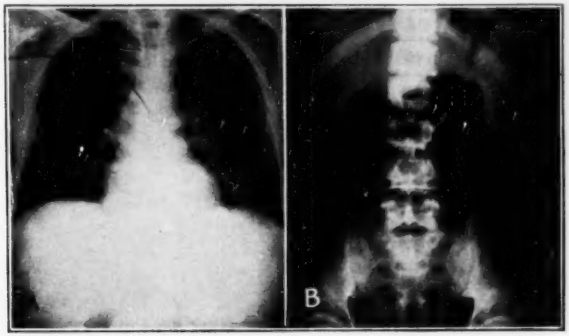


Fig. 1.—*A*, preoperative upright anteroposterior roentgenogram of the chest showing elevation of the left leaf of the diaphragm. *B*, preoperative upright scout roentgenogram of the abdomen showing a large, oval, well circumscribed area of increased density in the left upper quadrant. The gastric air bubble has been displaced medially. There are irregular serrations along the greater curvature of the stomach. The slightly dilated large bowel is seen occupying a central position in the abdomen and is surrounded by an area of increased density suggesting intra-abdominal fluid. A similar density may be seen between the few loops of slightly distended small bowel. Free intra-abdominal fluid is also suggested by the homogenous increased density extending from the extra-peritoneal fat along the left gutter.

the normal size. There were numerous subcapsular hematomas present over its posterolateral surface. There was a large subcapsular hematoma at the lower pole which occupied approximately one third of the diaphragmatic surface. There was a 3 cm. tear through the capsule at its uppermost extent near the anterior border. Fresh blood was oozing from this area. Splenectomy was accomplished without difficulty by means of Balfour's technic. The abdominal incision was closed with interrupted cotton sutures. One thousand cubic centimeters of whole blood was given during the operative procedure. The patient left the operating room in excellent condition, without evidence of respiratory embarrassment or circulatory failure.

In the immediate postoperative period a malarial paroxysm manifested itself in a severe chill followed by a rise in temperature to 106 F. Quinacrine hydrochloride therapy was instituted immediately, the parenteral route being utilized. A second malarial paroxysm occurred on the first postoperative day, at which time P. vivax was again demonstrated in smears of the peripheral blood. Repeated

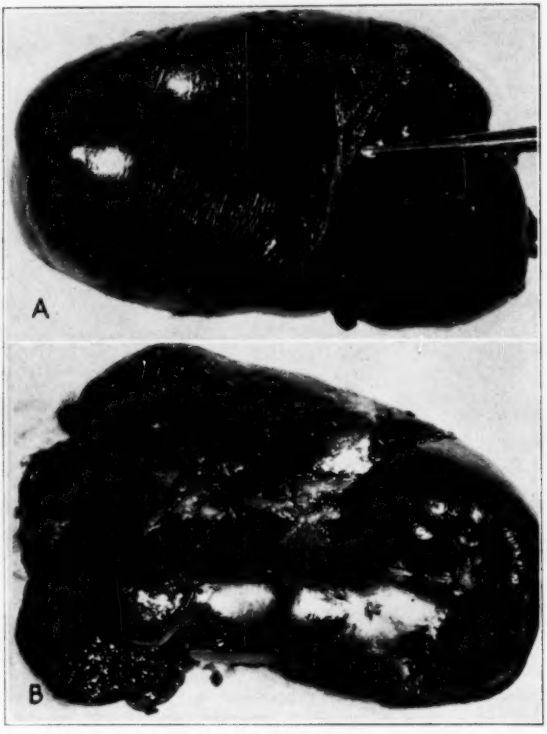


Fig. 2.—Photograph of surgical specimen. The spleen measured 18 by 12 by 12 cm. At the operating table the capsule seemed under extreme tension. The organ was a deep bluish red and seemed to be less firm than the normal spleen in situ. Several subcapsular hematomas could be seen, the largest of which was located at the lower pole on the posterolateral surface. It measured 8 cm. in diameter and 2.5 cm. in thickness. *A* shows the splenic capsule turned back exposing the hematoma. The pointer demonstrates the approximate site of capsular rupture. The hilar surface *B* likewise showed several small subcapsular hematomas.

examinations since that time failed to show malarial parasites. Levine suction was continued for four days, during which time the patient was maintained on intravenous infusions of dextrose in isotonic sodium chloride solution, whole blood, plasma, amino acids and vitamins. A nonproductive cough, associated with signs of consolidation in the left lower pulmonary field, developed on the third

postoperative day. Stereoscopic roentgenograms of the chest led to the diagnosis of atelectasis of the lingular portion of the upper lobe in the left lung. This responded to conservative management, including frequent vigorous coughing, deep breathing exercises, administration of penicillin and ambulation. After discontinuance of gastric suction a modified liquid diet was tolerated. A soft diet was permitted on the fifth postoperative day and a full diet on the eighth day. The patient was made ambulatory on the third postoperative day. Healing of the wound was uncomplicated. He was discharged from the hospital on the fourteenth postoperative day without any complaints. At the time of his release the red blood cell count and the hemoglobin content were within normal limits.

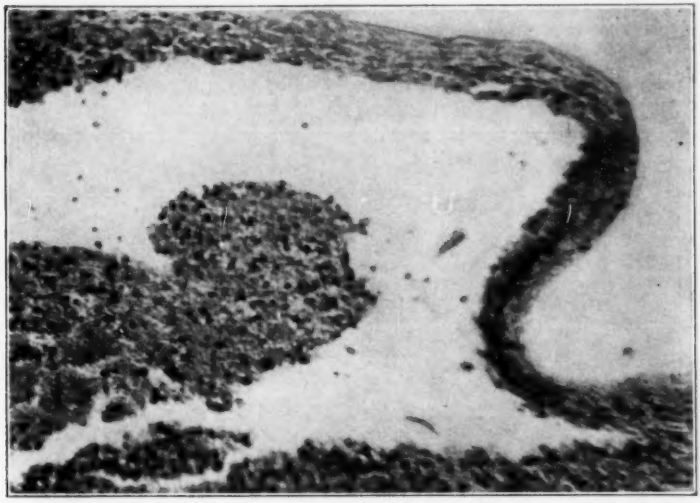

Fig. 3.—Photomicrograph of a section taken through the subcapsular hematoma near its periphery. Note how the developing hematoma has dissected the splenic capsule from the pulp.

Pathologic examination of representative sections through the spleen revealed a decided proliferative reaction of the splenic corpuscles (figs. 3 and 4). Evidence of toxic necrosis and depletion of the lymphoid tissue was noted. A great deal of malarial pigment was found deposited in the splenic pulp. Generalized fibrosis was present. Many parasitized erythrocytes were identified in small vessels and capillaries. Sections through the capsule revealed many small subcapsular hematomas. Figure 3 shows how the developing hemorrhage dissects the thickened splenic capsule from the pulp.

## COMMENT

Beyond all doubt this represents a case of spontaneous rupture of a malarial spleen during a relapse of P. vivax malaria. There are several points illustrated which are of more than casual interest. Undoubtedly the subcapsular hematomas found at the time of opera-

tion had begun to form two weeks before the patient's admission to the hospital. I believe these to have been the explanation of the intermittent attacks of sharp pain in the left shoulder. Clinicians should be aware of splenic rupture, whether they are dealing with induced malaria or with acquired malaria, when clinical enlargement of the spleen is noted, accompanied with pain in the left shoulder. Rebound tenderness, with referral of the pain to the left shoulder, may be of value in making the diagnosis of splenic rupture, regardless of the cause.

## SUMMARY

Evidence is cited from the literature and from a case reported to support the increasing incidence of spontaneous rupture of diseased spleens. It is suggested that there will be a further increase in the incidence of rupture of malarial spleens in view of the growing reports of relapsing vivax malaria of Pacific origin in veterans.

The pathologic changes in malarial spleens and the pathogenesis of their spontaneous rupture by two mechanisms are discussed in relation to previous reported cases and the pathologic findings in the accompanying case.

The outstanding clinical features are reviewed. Two clinical signs are emphasized. The first, intermittent attacks of pain in the left shoulder during a malarial relapse, should suggest the possibility of

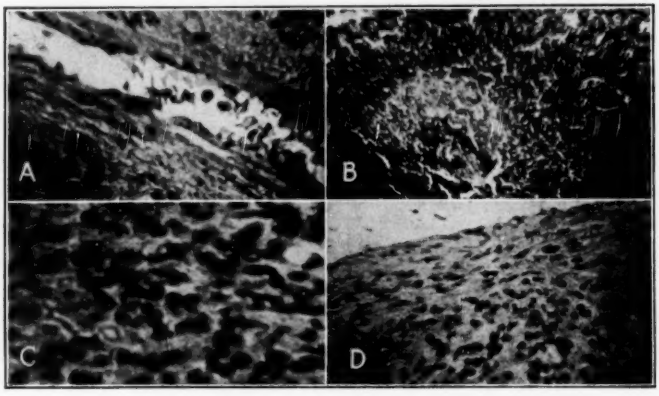


Fig. 4.—Photomicrographs of representative sections through the splenic pulp. Fixation in Zenker's solution (without acetic acid) Stained with hematoxylin-eosin azure II. *A*, many parasitized erythrocytes in a small vessel. *B*, proliferative reaction of a splenic corpuscle. Early toxic necrosis is in evidence. *C*, large amount of malarial pigment deposited through the pulp. *D*, generalized fibrosis and a greatly thickened capsule were found in all sections which were studied.

the development of subcapsular hemorrhage. The second, rebound tenderness with referral of the pain to the left shoulder, is an aid in the diagnosis of splenic rupture, regardless of the cause.

The importance of competent roentgenologic assistanc in the diagnosis is emphasized. Laboratory tests which may prove helpful in the evaluation of the patient's condition are listed.

It is pointed out that there is no question regarding treatment, splenectomy being the only method of controlling the hemorrhage. The preferred approach is given. Certain adjunct therapy, in particular that applicable to the treatment of hemorrhagic shock, is evaluated.

One case is presented in detail. Many of the technical factors involved in the preoperative preparation, anesthesia, the actual surgical procedure and the postoperative convalescence are presented. A gratifying recovery was noted, the patient being discharged from the hospital two weeks after operation with no symptoms.

# SYSTEMIC ADMINISTRATION OF HEPARIN AND DICUMAROL® FOR POSTOPERATIVE ADHESIONS

## An Experimental Study

MAURICE M. DAVIDSON, M.D.
ROSELLE PARK, N. J.

HERTZLER studied the peritoneum for many years and came to the conclusion that to prevent adhesions is to prevent healing. However, numerous investigators have utilized every imaginable modality, physical and chemical, to control the pathologic effects of adhesions. Many of the methods of procedure have been impractical and the results controversial.

In recent years, Ochsner and others experimented with digestive enzymes such as papain, claiming reduction in postoperative complications due to adhesions. Yardumia and Cooper advocated the use of pepsin intraperitoneally for the same purpose. Other digestants such as trypsin have also been tried.

The utilization of amniotic fluid concentrate (i. e., amfetin) as a stimulator of the peritoneal defense mechanism was investigated by Johnson, Warren, Lacy, Rea and Wangensteen, and favorable reports were published. Larson and Halverson introduced sodium ricinoleate as a peritoneal stimulant. Bargen, Judd, Waldron and Steinberg proposed peritoneal immunization with killed vaccine suspensions of Escherichia coli. Seeley later studied the comparative stimulant effects of distilled water, amniotic fluid, Bargen's vaccine and 2 per cent sodium ricinoleate by estimating the influx of polymorphonuclear cells into the peritoneal fluid and found that the figures were 19 per cent in six hours for distilled water and 36, 51 and 72 per cent respectively in three hours for the others.

Seeley stated that sodium ricinoleate caused an outpouring of exudate rich in neutrophils and monocytes, supplied fluid volume for lubrication and resulted in rapid phagocytic absorption of fibrin and regenerative

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Research project presented to the Department of Graduate Surgery of the New York Medical College, Flower and Fifth Avenue Hospitals, New York city, in application for a degree in surgery.

This project was approved by the Research Committee at its meeting of Jan. 26, 1945, for investigation. Part of this work was done in the Graduate Department of the college with the cooperation of Dr. J. H. Fobes, the director.

healing. Wangensteen reported on the use of 1 per cent ricinoleate in gastrointestinal anastomosis, with a 70 per cent preventative effect on the formation of postoperative adhesions.

Sweet was of the opinion that peritoneal stimulants and digestants are of questionable value.

Steinberg introduced coli-bactragen® (a tragacanth suspended vaccine) into the peritoneal cavities of 150 dogs, without adhesions forming. However, he stated that in some of the animals treated in the later stages of peritonitis, when damage to the tissue had already been incurred, adhesions did develop.

In 1941 Lehman and Boys reported on the use of heparin in the peritoneal cavity for the prevention of adhesions. Experimenting with dogs, they introduced 10,000 units of this drug in 300 cc. of isotonic sodium chloride solution followed by 5,000 units in the same amount of solution every twelve hours for a total of 40,000 units in three and a half days. They also reported on the intraperitoneal use of heparin in 14 human beings, with 1 death. They cautioned that the greatest potential hazard was hemorrhage.

Massie, reviewing the work of these authors, mentioned that experimental animals and controls were examined at the end of six weeks. When no drug was used, an incidence of adhesions of 130 per cent was found. In dogs in which isotonic sodium chloride solution, amniotic fluid and papain were utilized, an incidence of over 100 per cent was found. When heparin was employed, adhesions occurred in only 34 per cent. He advised the administration of 10,000 units every twelve hours for a total of 40,000 units in thirty-six hours. Seven cases involving human beings were reported in which good results were obtained. Massie cautioned that careful studies of the blood and clinical observations were required to guard against fatalities from hemorrhage and delayed healing of wounds.

Preliminary investigations in this project were directed along the following lines of thought:

A. An attempt was made to devise a practical method of keeping visceral and parietal peritoneal surfaces separated long enough for healing to occur. With pneumothorax and pneumoperitoneum in mind, it was thought that gas could be employed effectively, and in a similar manner postoperatively, to control the formation of adhesions. Furthermore, it seemed just as practical to give continuous intraperitoneal infusions of isotonic sodium chloride solutions and other fluids after operation as to give them intravenously. In addition, the mechanical and lubricating effects would be usable. The action of heparin infusions could also be studied.

B. An attempt was made to control the formation of fibrin by the systemic use of the newer anticoagulants, especially heparin and dicumarol.

The consideration that healing of wounds might be delayed in proportion to the limitation in the formation of adhesions was entertained. However, it was thought that early ambulation could be employed to affect the balance in favor of control of the adhesions, although sutures might have to be left in longer to prevent disruption of the wound.

At this point it might be well to review briefly the mechanics of the formation of intraperitoneal adhesions.

Histologically, the peritoneum is a three-layered membrane consisting of (1) a single cell layer of pavement epithelium, (2) a basement membrane of parallel connective tissue fibers plus cement substance and (3) an areolar connective tissue layer varying in density with the mobility of the viscera in different localities and carrying a network of blood and lymph vessels.

Anatomically, the chief concern is with the distribution of the parietal and visceral peritoneal linings, both normal and anomalous, and the mobility and configuration of the greater omentum. It should be remembered that these linings are everywhere contiguous.

Physiologically, two factors are particularly important in this connection. First, the peritoneum supplies mechanical lubrication to facilitate visceral mobility and function. Secondly, the absorptive capacity of the peritoneum is tremendous. Hertzler has shown that if a quantity of isotonic fluid up to 10 per cent of the body weight is instilled intraperitoneally, 30 per cent will be absorbed in one hour and up to 70 per cent in two hours. Use of hypotonic and hypertonic solutions did not alter these figures materially after osmotic equilibrium was reached. Accurate figures on the rates of absorption of gases were not obtainable although it is generally known that carbon dioxide, oxygen and nitrogen are more readily absorbed in the order given.

Pathologically, the origin of adhesions is always traumatic, whether they are due to chemical, physical, bacterial or toxic (malignant) injury. Immediately after injury to the endothelial cell layer there is an exudation of serum and fibrin. In two hours fibrin agglutination occurs. Firm bands are found in eighteen hours. Organization begins after the third day, with the transition of fibrin to connective tissue complete in six to eight days (Steinberg).

According to Hertzler, there are two types of adhesions, temporary and permanent. In the former there is no change in the basement membrane. Phagocytosis plus enzyme lysis causes spontaneous release in a few hours. This is a purely salutory process, nature's method of

limiting infection and inflammation. In some cases when these adhesions persist for longer than a few days they become much attenuated and may disappear later. In the case of permanent adhesions forming, however, there has been a permanent injury to the endothelium, with the formation of definite fibrin bridges which later become organized in firm connective tissue. Prenatal adhesions (so-called fetal peritonitis) are simple alterations in the development of serous surfaces and are usually of no pathologic consequence.

Surgically, the tendency of adhesions to form varies markedly in different animals and in the same animal under different conditions. The process appears to be related to the ability of the animal to form fibrin and lytic heparin-like substances in the intracellular fluids.

It is axiomatic that adhesions have no surgical significance unless they produce obstruction or other visceral disease.

The role of the greater omentum is important surgically and pathologically. It is practically always found adherent to previous peritoneal wounds, especially to incisions, and is frequently the cause of obstruction. It may be removed with impunity, and this has been suggested as a prophylactic measure. However, it has a definite useful function in the limitation of infection, encapsulation of foreign bodies and sealing of postoperative visceral wounds.

The second part of this project was concerned with the use of heparin and dicumarol systemically in retarding the formation of fibrin, with the hope that the incidence of adhesions would be reduced.

Heparin, a mucoitin polysulfuric acid in combination with acetic and glycuronic acids, is derived mainly from the mast cells of the liver and lungs. The first record of its anticoagulant properties was made by McLean. Howell purified it and worked on it until 1929. Best, of Toronto, later became interested in this substance and standardized its action quantitatively and physiologically. It is found normally in the circulating blood and is antagonized in the same medium by thrombokinase and trypsin. It is thought to have these main actions in vivo: 1. It inhibits platelet agglutination and prolongs coagulation time. 2. It prevents the conversion of prothrombin to thrombin. 3. It has a direct antithrombic action. The effect of heparin is manifested immediately on injection and persists for three or four hours. It does not affect fibrin already deposited, as in thrombus, nor does it affect osmotic pressures, red or white blood cells, hematocrit values, or antigens. Heparin is available commercially in solutions of 10 mg. per cubic centimeter (1,100 Toronto units), which quantity is sufficient to keep 5,000 cc. of plasma in vitro liquid for four hours at 37 C.

Heparin may be given intravenously, subcutaneously or intraperitoneally. For optimal effects the coagulation time should never fall

below 15 minutes or exceed 40 minutes (Lee-White method). Best and Murray have administered heparin by continuous intravenous injection (according to Prandoni) at the rate of 20 to 30 mg. per hour. Allen gave 50 mg. and repeated the same dose every four hours using an interrupted intravenous method. Evans and Boller are proponents of subcutaneous administration, using the Pitkin menstruum as a vehicle. The latter substance is composed of 18 per cent gelatin, 8 per cent dextrose and 1 to 1.5 per cent acetic acid in distilled water and serves to liberate the heparin much more slowly. Ampules containing 100 mg. of heparin per cubic centimeter of menstruum with or without vasoconstrictors added are obtainable. The average duration of effect with the former is forty-one hours and with vasoconstrictors ephedrine and epinephrine) added sixty-one hours. Evans and Boller give 1 cc. of each for the first dose to a 150 pound (68 Kg.) patient. They also administer 200 mg. of dicumarol at the same time and then maintain the patient on about 100 mg. of dicumarol daily. Bauer has given 150 mg. of heparin every four hours intravenously and encountered no intra-abdominal, subcutaneous or other serious bleeding except for hematuria, which stopped in two or three days. Intraperitoneal administration has been described previously.

Dicumarol, $C_{19}H_{12}O_6$ or 3, 3'methylene-bis-(4 hydroxycoumarin), was isolated and synthesized by Link in 1940. When given orally its action is to produce hypothrombinemia. The disodium salt has been used intravenously for the same purpose. Dicumarol prolongs the prothrombin time, increases the sedimentation rate, impairs clot contractility and in large doses prolongs coagulation time. The anticoagulant activity of dicumarol is delayed until there is a considerable reduction in free blood prothrombin, which takes from twenty-four to forty-eight hours. The first dose is figured on the basis of 2 mg. per pound (average, 300 mg. in human beings). Successive doses must be based on the prolongation of the prothrombin time over the normal, which is from 10 to 15 seconds. The Quick method is used most frequently, and the result is best expressed in percentage of normal. Bleeding rarely occurs when the prothrombin time is 10 per cent or more, and thrombosis is retarded when it is over 30 per cent of normal. Dicumarol has a cumulative action which may carry over for many days, and its dosage is not related to age and weight. Its site of action is unknown, and it has no anticoagulant action in vitro.

The experimental investigations which are to be described were carried on over a period of about three years. A total of one hundred and eight procedures was performed on 37 mongrel dogs varying in weight from 18 to 42 pounds (8.2 to 19.1 Kg.). The youngest animal was about 3 months old and the oldest over 8 years.

The investigation was carried on in two parts. First, it was planned to study the mechanism of the formation and control of adhesions by repeating procedures already described in the literature. The second part was devoted to the attempt to limit the production of adhesions by administering heparin and dicumarol systemically.

The modern surgical principle of early ambulation was perforce utilized throughout. The only animals to which this did not apply were those kept partially anesthetized during prolonged intraperitoneal infusion procedures.

## PART ONE

This was devoted to the study of (*a*) peritoneal closure and constricting dressings and (*b*) intraperitoneal instillation of gases and liquids. Thirteen dogs were subjected to a total of fifty-seven operative procedures.

*A. Peritoneal Closure and Constricting Dressings.*—The observations on method of peritoneal closure and type of dressing were considered as part of the instillation operations, except when gases and heparin were used intraperitoneally. Twenty-eight procedures considered in groups of seven were performed. Two methods of peritoneal closure were employed. In the first two groups the usual continuous approximation suture was used. The remaining peritoneal closures were effected by interrupted sutures placed about ½ inch (1.27 cm.) apart, with careful eversion of the peritoneal edges. In all cases the greater omentum was pulled down and interposed between the viscera and the incison. The effect of constricting abdominal dressings was observed simultaneously by utilizing them in groups 1 and 3.

A preliminary operation was performed on each dog for the purpose of producing adhesions. No special preoperative or postoperative supportive measures other than routine feeding and watering were used. Each animal was given a proportionate dose of morphine sulfate hypodermically to quiet it and then anesthetized with intravenously administered thiopental sodium (pentothal sodium®), occasionally supplemented with open cone ether. Epilation was performed chemically by a saturated solution of barium sulfide and the skin prepared with soap, ether, iodine and alcohol. Aseptic technic was followed as closely as possible. A midline celiotomy through a 4 or 5 inch (10 to 12 cm.) incision was then performed. Careful exploration was carried out and particular notice taken of congenital or other preexisting adhesions or bands. The presence of existing inflammatory processes, especially pyometra (canine salpingometritis) was also noted on the animal's record card. A loop of bowel was picked up and the serosa rubbed vigorously with dry gauze until it was red, and 2½ inch (6 cm.) marker sutures of white cotton were then placed at each end of the traumatized area and the

loop dropped back into the abdominal cavity. The wound was closed in three layers, chromic gut for the peritoneum, interrupted cotton sutures in the fascia and continuous subcuticular plain gut for the skin. Particular attention was paid to the method of peritoneal closure (to be described later). The wounds were then sealed by painting with rubber cement and applying crinoline in successive layers and either covered with a circular moderately constricting bandage or reenforced with short straps of flamed adhesive.

The results of these twenty-eight observations were as follows:

Group 1 (7 cases; continuous peritoneal closure and constricting bandage). In this group there were firm adhesions between the peritoneal scar and the greater omentum in every case. In 3 instances loops of bowel were found adherent in addition.

Group 2 (7 cases; continuous peritoneal closure and wound sealed with rubber cement and crinoline). Visceroparietal adhesions were seen in 4 instances. The adhesions appeared less firm and more elastic.

TABLE 1.—*Influence of Method of Peritoneal Suture and Type of Wound Dressing on the Incidence of Visceroparietal Adhesions*

| Type of Suture and Dressing | Incidence of Visceroparietal Adhesions, % |
|---|---|
| Group 1 (continuous suture plus constricting dressing) | 100 |
| Group 2 (continuous suture plus wound seal) | 57 |
| Group 3 (interrupted, everting sutures plus constricting dressing) | 71 |
| Group 4 (interrupted, everting sutures plus wound seal) | 28 |

Group 3 (7 cases; interrupted, everting peritoneal closure and constricting bandage). Visceroparietal adhesions were found in 5 cases, an improvement over group 1. The adhesions were short and firm as in group 1, however.

Group 4 (7 cases; interrupted peritoneal closure and wound seal). Adhesions between the omentum or the bowel and the peritoneal incision were seen in only 2 instances. They appeared longer and more elastic, similar to those in group 2.

Conclusions: 1. Careful eversion of the incised peritoneal edges in the closure of wounds tends to decrease the incidence of visceroparietal adhesions. The continuous over and over suture, particularly if placed under tension, leaves a visceral edge of raw peritoneum and suture material to which intra-abdominal structures are prone to adhere. 2. The common practice of applying constrictingly long straps of adhesive postoperatively should be discouraged. This tends to press together the raw parietal and visceral wounds and encourages the formation of dense short adhesions capable of producing a pathologic

process. 3. Best results were obtained in this group of procedures when the peritoneum was carefully everted and a simple wound-sealing dressing was applied.

No mention is made of the incidence of viscerovisceral adhesions at this time. They occurred practically 100 per cent of the time and are to be discussed further in detail.

*B. Intraperitoneal Instillation of Gases and Liquids.*—The original group of 13 dogs were subjected to forty-four procedures. The operative technic used was the same as before with the exception that suturing bites were placed close together to produce leak-proof closures. Incisions were made through the right or left rectus muscle parallel to the original scar. A record was made of all adhesions found; they were then carefully separated and peritonealized as much as possible. Just prior to peritoneal closure, a 1 inch (2.5 cm.), 20 gage needle was inserted parallel to the abdominal wall under direct vision beside the

TABLE 2.—*Effect of Intraperitoneal Administration of Gases on Adhesions*

| Name of Gas | Amount, Cc. | No. of Cases | Incidence of Visceroparietal Adhesions, % | Incidence of Viscerovisceral Adhesions, % |
|---|---|---|---|---|
| Carbon dioxide | 300 to 500 | 3 | 33⅓ | 100 plus |
| Oxygen | 300 to 500 | 3 | none | 100 plus |
| Air | 300 to 500 | 6 | none | 100 plus |

wound. The peritoneum was closed as described and a wound seal dressing applied without constriction of the abdominal wall.

1. Instillation of Gases (Twelve Procedures). From 300 to 500 cc. of carbon dioxide, oxygen and air, measured by water displacement from a double glass-tubed, rubber-stoppered jar, was instilled immediately after operation through the perforating needle. The injection was stopped as soon as the abdominal wall appeared moderately distended or gas could be detected hissing through the sound seal. The theory of the experiment was based on the principle of pneumothorax; it was hoped that the results would be comparable.

Carbon dioxide was used in three procedures, oxygen in three and filtered air in six. The first gas seemed to absorb in six to eight hours and the second in about nine to twelve hours, but air kept the abdomen somewhat inflated for twenty-four to thirty-six hours.

There was a marked reduction in the incidence of visceroparietal adhesions but no effect on viscerovisceral ones.

2. Instillation of Liquids (Thirty-two Experimental Procedures). Normal isotonic sodium chloride; dextrose, 5 per cent in distilled water; gelatin, 6 per cent and in gel form, and heparin in three forms of solution were employed. On account of the tremendous absorptive

power of the peritoneum, it was decided to test it first in the individual animal and then to attempt to retard it by the use of high molecular weight solutions such as gelatin and finally to employ the fibrin-inhibiting heparin in order to evaluate properly subsequent findings.

As a result of the information previously obtained, the peritoneal incisions were all closed, with careful eversion of the edges and the wounds sealed without constriction.

(*a*) Isotonic sodium chloride solution was administered immediately after closure through the intra-abdominal needle and subsequently for ninety-six hours in two procedures. Both animals used were kept lightly anesthesized throughout by the addition of small amounts of thiopental sodium to the infusions. Twenty-four hour fluid requirements were estimated on the basis of 20 cc. per pound minimally. Half of the total amount was injected at once and the remainder given by continuous clysis. Further checks on the capacity of the dogs to absorb the fluid were made on the basis of estimates of urinary specific gravity, the average canine variation being from 1.020 to 1.066. It was anticipated that some edema might develop from the excess of chlorides. However, it was thought that this factor might tend to delay peritoneal absorption to some extent.

Preputial edema was noted on the third day of the continuous infusion in 1 animal and on the fourth day in the other. The urinary specific gravity was maintained between 1.010 and 1.028 (indwelling catheter specimens) by administering 40 cc. per pound of isotonic sodium chloride solution (with 0.25 per cent thiopental sodium). Toward the end of the ninety-six hour period signs of pulmonary edema followed shortly by tetanic spasms developed in the first animal, and it died. The second dog was reoperated on nine days later.

In case 1 (post mortem) there were notable edema of all tissues, some free fluid in the peritoneal cavity, slight agglutination between the greater omentum and the small bowel which separated easily on manipulation and no evidence of formed adhesions. The fact that this animal formed no adhesions was not considered too significant, however. The altered metabolism in toxic animals was found to be associated with fibrinolysis on many occasions and will be discussed again.

In case 2 there were no adhesions of the peritoneum of the incision to the viscera. Visceral adhesions, however, recurred 100 per cent.

(*b*) With the use of the same method, 5 per cent dextrose in distilled water was infused in five procedures. No edema occurred in any of the cases during the ninety-six hour period. Reoperation was performed on the ninth to the fourteenth day. There was a marked reduction in visceroparietal adhesions in all except 1 animal. In this animal pelvic peritonitis developed from a preexisting pyometra, and

of course there were massive adhesions. Viscerovisceral adhesions reformed in all the other cases as well and to a greater extent than before.

It was concluded from these observations that the intraperitoneal infusion of isotonic solutions, with or without the occurrence of tissue edema, did not prevent or inhibit the formation of adhesions per se. The reduction in the incidence of visceroparietal adhesions was comparatively the same as could be expected from the utilization of early ambulation, nonconstricting wound dressings and intraperitoneal gases as described before.

(*c*) Gelatin in 6 per cent solution and in gel form was employed intraperitoneally. Both preparations were made from dehydrated sheet gelatin in distilled water and then sterilized. It was thought that peritoneal absorption would be retarded by a high molecular weight solution for a sufficiently long period to permit healing to occur with possible diminution in extent of adhesions.

Gelatin in 6 per cent solution was administered intraperitoneally to 4 animals by the same method as the fluids described. It was noted that the abdomen in some cases was slightly to moderately distended during the four day period of infusion. Percussion revealed dependent dulness, which could not be elicited when isotonic sodium chloride solution was used. In addition urinary specific gravities remained at a much higher level, varying from 1.032 to 1.050. These observations were indicative of retarded absorption.

Reoperation was performed in twelve to seventeen days.

There was free fluid in the peritoneal cavity in 2 dogs. The amount was, at the most, about 2 ounces (60 cc.), and it appeared similar to ascitic fluid in character. Visceroparietal adhesions were found in 1 case (25 per cent). Viscerovisceral adhesions, though they were seen in all cases, appeared to be reduced about 50 per cent in quantity and in firmness.

These observations would indicate that high molecular weight solutions such as 6 per cent gelatin would tend to combat the formation of visceroparietal as well as viscerovisceral adhesions. This tendency seemed to manifest itself despite the opposing coagulant action of gelatin on blood. Perhaps this effect can be explained on the grounds that the mechanical lubricating fluid action resulting from retarded peritoneal absorption, assisted by peristalsis, counteracts to a certain degree the normal agglutinating tendency of gelatin to precipitate fibrin, a precursor of adhesions. The following experiments in which gelatin gel was used and an opposite effect obtained would seem to bear this out.

In four procedures gelatin gel (25 per cent in distilled water), 100 cc., was applied to all raw surfaces just prior to closing the peritoneum. No infusions were given. In 1 animal severe gastroenteritis developed

twenty-four hours postoperatively, and it died four days later from wound dehiscence with evisceration. In this case there was a minimum of adhesions, but there was also poor healing just as in other animals dying in toxemia and shock.

The findings here could not be regarded as having any special bearing on the problem since reoperation revealed reformation of viscerovisceral and visceroparietal adhesions in all of the other 3 dogs. It was noted that the gelatin had been completely absorbed and that despite the known clotting action of this substance there was apparently no pronounced increase in adhesions over what would otherwise be expected.

(*d*) Heparin in three types of solution was infused intraperitoneally in seventeen procedures. Isotonic sodium chloride solution was used as a vehicle in three, 20 per cent gelatin in seven and Pitkin's menstruum in seven.

Heparin in isotonic sodium chloride solution was given after operation by the method of Lehman and Boys to 3 animals selected because they were known to have massive adhesions. Two of these dogs had been operated on three times and 1 four times. Three hundred cubic centimeters of isotonic sodium chloride solution containing 10,000 units of heparin was introduced intraperitoneally immediately after operation. Twelve hours later 5,000 units in 300 cc. of sodium chloride solution was given, and this was repeated every twelve hours until 40,000 units of heparin had been administered over a seventy-two hour period.

Coagulation time was checked by the Lee and White method at varying intervals after each infusion. Each time 1 or 2 cc. was aspirated through the intraperitoneal needle and observed for evidence of intraperitoneal bleeding. Two sets of observations were made.

1. After the first infusion, the blood coagulation curve varied from a low of 8 minutes to a peak of 19 minutes (the normal canine coagulation time being 6 to 8 minutes). This peak was attained in from two to two and a half hours after the infusion, and the value returned to normal in an average of about five hours.

After subsequent infusions using half the amounts of heparin, the blood coagulation curve rose to a high point of 13 minutes in about two hours and returned to normal in about four hours. There was apparently no residual or cumulative effect from the preceding administration of heparin.

The periods of decreased clotting were therefore of five and four hours' duration respectively, alternating with periods of normal coagulation of seven and eight hours.

2. Peritoneal fluid could be aspirated for the first two hours only because of the rapidity of absorption. The peritoneal cavity was therefore subsequently irrigated with 100 cc. of isotonic sodium chloride

solution at four hour intervals to check for bleeding. A Talqvist chart was used as a standard of comparison. It had been previously determined that after standard operative procedures one might expect a normal serosanguineous exudate color of about 10 per cent on the chart after irrigation with 100 cc. of sodium chloride solution during the first twenty-four hours in most cases. Therefore, any color intensity exceeding that in the irrigation returns was taken to be a proportionate estimate of bleeding.

Reoperation after healing of the wound gave the following findings: Visceroparietal adhesions were definitely reduced. One animal had none, and the other 2 had slight adhesions to the incision or to the area that had been perforated for the infusions. Viscerovisceral adhesions were definitely reduced to about half of what could normally be anticipated. In addition the adhesions found were longer and more tenuous and elastic than before.

Peritoneal aspirations revealed slight to moderate bleeding in all cases two hours after the initial large dose of heparin. In no case, however, did the color reading exceed 40 per cent on the Talqvist chart. Even when bleeding was noted after the subsequent infusions with adjusted dosage, it seemed to decrease gradually so that from six to eight hours postoperatively the color was practically normal.

The fact that some oozing did occur did not affect the findings. Apparently heparinized blood differs from normal to the extent that it is absorbed from the peritoneal cavity without contributing to the formation of adhesions.

Heparin in 20 per cent gelatin was used in seven procedures. It was thought that gelatin might serve to retard the liberation of heparin and afford a method of simplification of the method described before. (These experiments were performed prior to the reported successful use of Pitkin's menstruum as a vehicle in the literature). It may be noted in passing that heparin added to relatively viscous gelatin seems to increase its fluidity, facilitating its administration through a medium gage hypodermic needle.

Total preliminary dosage was calculated on the basis of 3 mg. (or 0.33 cc.) per pound on a twenty-four hour schedule. This amount of heparin in 10 cc. of 20 per cent gelatin was applied to the traumatized areas of peritoneum immediately after operation by paracentesis. The abdomens were gently kneaded to spread the medication. Four hours later, blood coagulation times were checked by the capillary tube method. If the coagulation time was less than 15 minutes, an additional proportionate amount of the same preparation was given.

The revised estimated dosage of heparin in gelatin was then reinjected at twenty-four hour intervals for a total of ninety-six hours in the same manner. Blood coagulation times were then taken at twelve

hour intervals. It was observed that decreased amounts of this preparation were required on the third and fourth days to maintain a 15 minute coagulation period, indicating that the gelatin was holding the heparin over the twenty-four hours.

In 2 of these animals signs of peritonitis developed, with temperatures of 105 F. and over (normal temperature of dogs varies between 99.5 and 102.2 F.). Penicillin in oil was administered to both in dosages of 100,000 units once daily, with uncomplicated recovery in 1 and recovery with development of a fecal fistula in the other.

Three dogs exhibited clinical signs of internal hemorrhage, with a drop in hemoglobin content to 40 per cent in 1 case (normal hemoglobin content in the dog being from 60 to 65 per cent). It was interesting to note that with the reabsorption of the intraperitoneal heparinized blood this figure returned to almost normal in every case by the fourth day postoperatively. In no case was the coagulation time prolonged over 19 minutes. The animal with the greatest drop in hemoglobin had a concomitant blood coagulation time of 13 minutes.

All 7 dogs were reoperated on in twelve to sixteen days. The immediate impression on opening the abdomen in every case was that there was a notable reduction in the extent and density of adhesions over what could be normally anticipated. The animal with the fecal fistula had a moderate mass of omental tissue wrapped around the tract and holding the ileum to the parietal peritoneum. Otherwise, only few viscerovisceral agglutinations were seen, and these separated easily on manipulation. The other dog with resolved peritonitis had an adhesion of the omentum to the small bowel and an area of agglutination between the round ligament of the liver, the liver itself and the anterior abdominal wall.

Of the remaining 5 animals, only 1 exhibited visceroparietal adhesions to the incision. Two animals had no adhesions at all. The other 3 dogs had a minimal amount of visceral adhesions, and these were of the nature of easily separated agglutinations similar to the temporary adhesions described by Hertzler.

The successful use of Pitkin's menstruum as a vehicle for the slow liberation of heparin having been noted, it was decided to try it out in seven exercises after the method just described. The composition of this menstruum is 18 per cent gelatin, 8 per cent dextrose and 1 to 1.5 per cent acetic acid in distilled water. It is obtainable in concentrations of 100 mg. of heparin per cubic centimeter of vehicle with or without the addition of vasoconstrictors (epinephrine or ephedrine). Evans and Boller have described its usage by the subcutaneous route in the treatment of thromboembolic phenomena and reported that the average duration of effect was forty-one hours; when the preparation

with vasoconstrictors added was used, this effect was further prolonged up to sixty-one hours and more.

The initial precalculated dose of 3 mg. per pound was given by paracentesis as before. Subsequent amounts were given at twenty-four hour intervals when indicated by blood coagulation times of less than 15 minutes. It was found that on the average about three quarters of the amount used had to be reinjected at successive intervals in order to maintain the necessary prolongation of the clotting mechanism. The average duration of effect of heparin in Pitkin's base intraperitoneally appeared to be twenty-six hours, with a variation in these 7 cases of from eighteen to twenty-nine hours. These findings were comparable to those obtained when plain 20 per cent gelatin was employed. The menstruum used contained no vasoconstrictors, however.

It was noted that this preparation was more irritating to the peritoneum than the preceding one. All the dogs were considerably more distended, their abdomens were much more tender, they refused to get

TABLE 3.—*Effects of Intraperitoneal Administration of Heparin on Adhesions*

| Vehicle | Method of Administration | No. of Cases | Complications | Reduction in Adhesions, Percentage |
|---|---|---|---|---|
| Isotonic sodium chloride solution | Infusion | 3 | Mild bleeding, 100% | Visceroparietal, about 75<br>Viscerovisceral, about 50 |
| Gelatin, 20% (10 cc.)..... | Paracentesis every 24 hr. | 7 | Bleeding, 42%; infection, 27% | Visceroparietal, about 75<br>Viscerovisceral, about 75 |
| Pitkin's menstruum (1 cc.) | Same | 7 | Bleeding, 57%; infection, 71% | Visceroparietal, about 50<br>Viscerovisceral, about 50 |

up and move around even when prodded, 4 of them had frequent spells of vomiting and, in general, all had higher temperatures and acted sicker than before.

In 1 animal severe diarrhea developed on the third day, and it died on the fifth. Postmortem findings were similar to those noted before in toxic animals which died. There were few adhesions and little evidence of healing of the wound.

The incidence of complications parallelled that noticed when heparin in gelatin was utilized in the remaining 6 dogs. Peritonitis in 1 animal with chronic pyometra and infections of the wounds in 2 yielded promptly to penicillin therapy. In 4 cases evidence of internal hemorrhage was noted, with considerable serosanguineous discharge from the wound in 2. Blood coagulation time varied from 13 to 22 minutes.

When the dogs were reoperated on, again the first impression was that there was a considerable reduction in extent and nature of adhesions over what would normally be expected, but to a somewhat lesser degree than before. It was seen that the incidence of adhesions of the greater omentum to the area of paracentesis was more common, occurring in

4 of the cases. In 1 instance a loop of ileum was partially obstructed by an adhesive band. Visceral adhesions were also found in greater amounts. The general nature of the adhesions was similar to that seen in other heparinization procedures, although they were thinner, more tenuous and more elastic than those ordinarily found. It was believed that the greater irritation of the peritoneal endothelium by the menstruum somewhat counteracted the fibrolytic action of the anticoagulant.

Despite careful hemostasis, capillary oozing even to the extent of mild intraperitoneal hemorrhage was frequent. However, this appeared to be self compensated by the rapid absorption of heparinized blood by the peritoneum. The blood hemoglobin content returned to normal shortly after termination of the heparinization. It is possible that the heparinized blood itself acts as a vehicle for the prolongation of action of the anticoagulant.

The finding of Laufman and Heller that heparinization did not interfere with healing of the wound could be corroborated. All wounds were healed by the seventh day except in the cases in which infection occurred. There was only 1 case of wound dehiscence, and that occurred in a toxic animal. Although the wounds appeared to contain less fibrin, the growth of fibroblasts was apparently not impeded.

## PART TWO

In view of the encouraging findings noted, it was decided to investigate the relative merits of administering heparin and dicumarol systemically in the attempt to inhibit the formation of postoperative adhesions. Certainly, if fibrin was the determining factor it seemed to be, then the retardation of its formation by the use of anticoagulants, by whatever route administered, should also be effective.

Accordingly, 24 dogs were subjected to a total of sixty-four experimental procedures to test the plausibility of this assumption.

Since Hertzler and others had already proved that all potential adhesions are evident by the fourth day after operation, a treatment period of ninety-six hours was again chosen. The technical details of early ambulation, careful peritoneal eversion in wound closure and noncompressing wound dressings, all having shown promise of being helpful, were also employed.

It was decided to administer heparin subcutaneously in Pitkin's vehicle and in 20 per cent gelatin, because this was most convenient and had been proved to be as efficacious as when given intravenously. Dicumarol was given orally in tablet form.

Preliminary procedures for the production of adhesions were repeated according to the method described. To assay the relative incidence of adhesions in the upper (supramesocolic) and lower

(inframesocolic) portions of the abdomen, as well as to study the relative tendencies of denuded and traumatized surfaces to adhere, a small area of serosa was dissected off and another larger area abraded in the upper as well as the lower portion of each dog's abdomen.

The work was subdivided into experiments on four groups of 16 animals each.

1. Heparin suspended in Pitkin's menstruum was used in the first group.

2. Heparin in 20 per cent gelatin was used in the second group.

3. Dicumarol was used orally in the third group.

4. A combination of heparin and dicumarol was employed in the last group of 16.

Group 1. Heparin in Pitkin's base was given subcutaneously in preestimated doses of 2 mg. per pound (0.5 cc. or 50 mg. per 25 pounds [11.3 Kg.]). No vasoconstrictors were employed. The first dose was injected one hour after the completion of the preliminary celiotomy. This interval was selected for two reasons: first, because it takes from one to two hours for the anticoagulant action to manifest itself by this method, and, secondly, this would permit enough time to elapse for firm clot retraction in order to minimize postoperative hemorrhage.

Blood coagulation times were checked at four hour periods for the first twenty-four hours and whenever indicated subsequently in an attempt to maintain the coagulation time at 15 minutes or over. The capillary tube method was used since this was less time consuming and easier to perform as well as being sufficiently accurate for all practical purposes.

Supplementary injections were given when indicated during the first day. Again it was found that proportionately smaller doses were required on the second, third and fourth days to maintain the necessary prolongation of coagulation, indicating that the duration of effect was over twenty-four hours. By calculating and comparing dosages, it was found that the average duration of action of heparin in Pitkin's vehicle was thirty-seven hours.

For the preliminary celiotomy in all the procedures in this part of the investigation a 5 inch (12.7 cm.) incision was made through the linea alba extending up to about 3 inches (7.6 cm.) below the xiphoid to avoid the peritoneal reflection over the falciform ligament of the liver. The serosa was denuded and abraded on the anterior aspect of the stomach and on a loop of small bowel. Just prior to closure a short piece of ureteral catheter was inserted into the abdomen through a stab wound for periodic irrigation to test for possible hemorrhage. The abdomen was then closed according to the manner described previously.

It was noted that a wide variation in coagulation times occurred, especially during the first twenty-four hours on an estimated dosage of 2 mg. per pound, the range being from 10 minutes up to 45 minutes. Several factors were thought to be responsible for this: first, the individual differences in speed of absorption; second, variations in the total amounts of the preclotting elements such as prothrombin, ionic calcium, thrombokinase, vitamin K and autogenous heparin, and, finally, variable hepatic function in the metabolism of these substances. Subsequent dosages were individually adjusted to give a final average deviation in coagulation times of 14 to 31 minutes for the ninety-six hour period.

Irrigations through the indwelling ureteral catheter with 100 cc. of isotonic sodium chloride solution were performed at four and eight hour intervals to test for hemorrhage. It was observed that little bleeding occurred by this method compared to the intraperitoneal administration of the same drug. In only 2 instances did the color chart readings exceed 20 per cent, and then only slightly. The coagulation times in these dogs were over 40 minutes at the time.

On reoperation after ten to twelve days the following observations were made: In 3 dogs hematomas had developed around the indwelling catheters. This was probably due to the fact that in these cases the perforation had been made through muscle, since none of the other animals with midline (fascial) punctures exhibited this complication.

Visceroparietal adhesions were found in 2 cases, an incidence of 12 per cent. In both instances the greater omentum was wrapped around the catheter and was slightly adherent to the adjacent peritoneal wound. In 1 a small pledget of gauze had been accidentally left in the abdominal cavity at a former operation and was found encapsulated in a large mass of omentum adherent to the uterus.

Visceral adhesions occurred in 9 instances, or 56 per cent. Practically all were limited to the denuded areas of stomach and small bowel. Omentum, other loops of bowel or falciform ligament was seen adherent to these spots. The adhesions were thinner, more elastic and more easily separable than would normally be expected, however, and no potentially obstructive kinks or bands could be found. The frequency of upper or lower abdominal adhesions to raw areas was about equal. No adherence of the areas of stomach or bowel which had been merely abraded was observed, although in 2 cases a long marker suture was enmeshed in other adhesions.

Review of the coagulation times indicated that the frequency of adhesions varied almost directly with the extent of prolongation of this factor inasmuch as the animals with no adhesions had a coagulation time of over 27 minutes, especially during the first twenty-four hours. In

the other 9 instances the clotting times were from 10 to 18 minutes the first day and from 14 to 35 minutes subsequently. It is apparent that the maximum prolongation of blood coagulation within the limits of safety during the first twenty-four hours gave the best results.

Postoperative hemorrhage did not occur with this method, probably for several reasons. With careful hemostasis and enough time lapse for firm clot retraction prior to heparinization, the increased blood fluidity offered no hazard in a closed vascular system. It is known that formed thrombus and capillary permeability are not altered by anticoagulants.

Group 2. Sixteen experiments were conducted with heparin in 20 per cent gelatin administered subcutaneously. The same method of procedure and dosage schedules as that used in group 1 was fol-

TABLE 4.—*Use of Heparin in Pitkin's Vehicle Subcutaneously*

| | |
|---|---|
| Dosage | Preliminary, 2 mg. per pound; subsequent, in proportion to fluctuation in coagulation time |
| Duration of effect—average, 37 hours | |
| Number of procedures—16 | |
| Coagulation times | First 24 hours, from 10 to 45 minutes; average over the 96 hour period, from 18 to 31 minutes. |
| Incidence of bleeding | Hematomas—intramuscular, 3 cases, or 18 per cent<br>Intraperitoneal oozing—2 cases, or 12 per cent<br>Frank hemorrhage—none |
| Findings | Adhesions markedly reduced; directly proportional to extent of prolongation of coagulation times especially during the first 24 hours; visceroparietal adhesions occurred in only 12 per cent; viscerovisceral adhesions seen in only 50 per cent of animals with denuded serosas and in less than 1 per cent of the others |

lowed. Greater care, however, was taken to place the piece of ureteral catheter through a fascial perforation and to fix the intra-abdominal tip by a suture in such a way as to permit minimal projection beyond the peritoneum.

As was expected, the findings in general were similar to those in group 1. The main difference noted was in the relative ability of the plain gelatin to retard heparin absorption in comparison to Pitkin's menstruum. Quantity for quantity, the latter is somewhat more efficient. Repeated checks of coagulation time indicated that the average duration of effect of heparin in gelatin was from eighteen to twenty-five hours and that the average variation for the ninety-six hour period was from 7 to 42 minutes for the entire group.

Only in 1 dog did a mural hematoma develop around the indwelling catheter and 2 animals showed evidence of frank intra-abdominal hemorrhage when the coagulation time was 23 and 38 minutes respectively.

Visceroparietal adhesions were found in 2 instances; in 1 they were between a denuded area of jejunum and the peritoneum in the area of the perforating catheter, and in the other the denuded area on the stomach and the upper end of the peritoneal incision were agglutinated together.

Viscerovisceral adhesions occurred in 11 cases, or 68 per cent, mainly between raw surfaces and contiguous omentum. Where the serosa had been abraded only, adhesions were found in 2 instances, or 12 per cent.

Group 3. Dicumarol was given orally to an experimental group of 16 dogs in which adhesions were known to have formed in previous experiments. The first dose of the drug was administered twenty-four hours preoperatively in each instance on the basis of 2 mg. per pound. Subsequently, 0.5 to 4 mg. per pound every twenty-four hours was given over a four day period.

TABLE 5.—*Use of Heparin in 20 Per Cent Gelatin Subcutaneously*

| |
|---|
| Dosage—same as in table 4 |
| Duration of effect—average, 21 hours |
| Number of procedures—16 |
| Coagulation times<br>Variation from 7 to 42 minutes for the 96 hour period. |
| Incidence of bleeding<br>Hematomas—1 case (less than 1 per cent)<br>Intraperitoneal hemorrhage—2 cases, or 12 per cent |
| Findings<br>Adhesions markedly reduced as before; visceroparietal adhesions occurred in 12 per cent (only in denuded areas); viscerovisceral adhesions occurred in 68 per cent in denuded places and only in 12 per cent in other areas |

In half of this group it was decided to test the influence of hepatic function on prothrombin time and dicumarol action by using chloroform as the anesthetic during the operation and for a variable time up to an hour afterward. In the remaining 8 cases the method of anesthesia used previously was repeated.

Since all the animals had already been subjected to at least one midline celiotomy, it was necessary to use right or left rectus incisions. The muscles were retracted laterally in each case rather than split in order to minimize bleeding. Ureteral catheters were introduced as before to serve as tap indicators for possible bleeding.

Prothrombin times were determined every twenty-four hours by the method of Quick and plasma prothrombin concentration noted in percentage of normal. Great difficulty attended the subsequent administration of dicumarol because of the wide variations and sudden fluctuations in these calculations of prothrombin time. Several preparations of the thromboplastin solutions used in the tests were tried, but these

differences persisted notwithstanding. It was found that the average prothrombin time was 5 to 7 seconds and that bleeding did not occur until it was prolonged over 32 seconds; in human beings the normal plasma prothrombin time is 15 seconds and bleeding can be expected when it exceeds 25 seconds.

The chloroform-anesthetized animals required much smaller subsequent dosages of the drug, and their prothrombin times were easier to control than those of the other dogs. This was indication of hepatic damage, since it is known that bleeding in jaundice is due to increased prothrombin time. Daily repeat doses varied from 0.5 to 1.5 mg. per pound in this group to maintain a plasma prothrombin concentration below 30 per cent of normal (also the critical figure used in antithrombosis therapy).

The remaining 8 dogs in this group required from 2 to 4 mg. per pound per day to maintain a similar prothrombin plasma level. This appears to indicate that dogs have several times as much prothrombin in their plasma as human beings, since the effect of dicumarol is cumulative and additive and clinical experience has shown that, proportionately, one third to one fifth as much of the drug is required to maintain this level in the latter species.

The mean prothrombin concentrations for the ninety-six hour period was from 0 per cent to 45 per cent of normal for the entire group. Bleeding occurred whenever the plasma concentration of this protein was below 5 per cent. Four animals died of uncontrollable intraperitoneal hemorrhage, 1 on the second day, 2 on the third day and 1 on the fourth day. The prothrombin levels in these animals before death were all at or near zero. Large doses of vitamin K were ineffective in checking the bleeding. Three additional dogs showed signs of intra-abdominal oozing and hematomas of the wound. These were of minor degree and relatively self limited and compensated.

Postmortem examination of the 4 animals dying of hemorrhage and shock revealed a minimal amount of visceral and parietal adhesions. None of the abraded areas appeared to be involved. In 2 instances the omentum was agglutinated to the denuded areas on the stomach. It seemed from the localization of the hematomas that hemostasis after denudation in these 2 cases had been inadequate.

The remaining 12 dogs were reoperated on after nine to twelve days. Visceroparietal adhesions were seen in 4 animals. In 1 the raw areas on the stomach, the greater omentum and the transverse colon were agglutinated together in one large mass at the upper angle of the incision. In the other 3 cases raw areas of stomach and bowel were implicated.

Visceral adhesions occurred in 8 instances, or 50 per cent. The attachments appeared as bulky edematous agglutinations, in contra-

distinction to the tenuous veluminous attachments seen when heparin was used. Again the denuded areas were mostly involved, although in 1 dog three loops of small bowel were attached to the uterus and adnexa while the denuded area of bowel was sealed with greater omentum.

It was the general impression that dicumarol was far inferior to heparin as an agent for the prevention of adhesions. Control of dosage in experimental animals was much more difficult. Laboratory procedures for checking dosage were more cumbersome also. The incidence of hemorrhage, partly because of these factors, was much more common and of much more serious importance. Finally, the occurrence of adhesions was considerably greater with dicumarol than with heparin.

Group 4. Heparin and dicumarol in combination were administered in sixteen procedures.

TABLE 6.—*Oral Administration of Dicumarol in Prevention of Adhesions*

| |
|---|
| **Dosage** |
| **Initial, 2 mg. per pound; subsequent, every 24 hours 0.5 to 4 mg. per pound** |
| **Number of procedures—16** |
| **Prothrombin concentration fluctuations—0 to 45 of normal** |
| **Incidence of bleeding** |
| **Hemorrhage—fatal in 4 animals, or 25 per cent; compensated in 3, or 18 per cent** |
| **Findings** |
| **Adhesions moderately reduced; visceroparietal adhesions found in 6 dogs, or 37 per cent; viscerovisceral adhesions found in 8 dogs, or 50 per cent (most adhesions occurred in connection with denuded areas)** |

The dicumarol was first given twenty-four hours before operation in amounts of 2 mg. per pound. This produced an average prothrombin time of 45 to 60 per cent of normal. The antifibrin effect was then exerted by injecting heparin in Pitkin's menstruum immediately after the incision was closed in the same dosage as had been used before, i. e., 2 mg. per pound. Anticoagulation was maintained by daily feeding of dicumarol in amounts of 2 to 4 mg. per pound checked against prothrombin concentrations.

The investigations were carried on by the same method used before. All the animals in this group had been operated on at least once and some three or four times. Their propensity for forming adhesions was a matter of record, so that fairly accurate conclusions could be drawn as to the efficacy of the experiments in preventing them.

The average prothrombin concentration for the entire group for the four day period was from 0 to 50 per cent of normal. Coagulation times checked twenty-four hours after the administration of heparin in Pitkin's menstruum ranged from 12 to 29 minutes.

Three animals died. One died on the fourth day from hemorrhage and shock, in another a large hematoma had developed in the incision on the third day and evisceration occurred on the sixth, and the third died in hyperpyrexia on the seventh day of an undiagnosed pathologic process. Postmortem examinations were performed on these animals and significant findings noted.

The other 13 dogs were reopened a week to ten days later and explored. In general, the observations made in the preceding set of experiments were reaffirmed. No material differences in the nature or extent of adhesions as a result of the heparin effect exerted over a twenty-four hour period could be seen. Although the adhesions in many instances appeared to possess greater transparency and tenuosity, their appearance was not nearly as remarkable as when heparin alone

TABLE 7.—*Administration of Heparin Subcutaneously and Dicumarol Orally for Adhesions*

| |
|---|
| **Dosage** |
| Heparin in Pitkin's base, one injection immediately after closure on basis of 2 mg. per pound |
| Dicumarol, first dose on basis of 2 mg. per pound started 24 hours preoperatively, with subsequent doses of 2 to 4 mg. per pound every 24 hours |
| **Number of procedures—16** |
| **Prothrombin concentration variations—0 to 50 per cent of normal** |
| **Coagulation time variations—12 to 29 minutes** |
| **Complications** |
| Three deaths; cause of 1 unknown, 2 from shock and hemorrhage (one of the dogs eviscerated) |
| **Findings** |
| Adhesions moderately reduced; visceroparietal adhesions noted in 5 cases, or 31 per cent; viscerovisceral adhesions noted in 9 cases, or 56 per cent |

was used over the longer period. Dicumarol seems to further the formation of bulky edematous agglutinations.

Visceroparietal adhesions were found in 5 animals, or 31 per cent. Viscerovisceral agglutinations occurred in 9 animals, or 56 per cent.

## COMMENT

Granted that the formation of postoperative adhesions is simply one aspect of the natural salutary process of repair, the relative frequency of pathologic sequelae intensifies the important significance of any agent or agents capable of limiting the extent of this process. The connective tissue cells which react to injury are the fibrocytes and the macrophages (histiocytes). Granulation tissue is produced by an ingrowth of fibroblasts and buds of endothelial cells into the exudate, producing a highly vascularized mass. As organization proceeds to completion, the connective tissue contracts with the deposition of collagen, and the capillaries decrease in size and number and mostly disappear, leaving dense pale scars or bands. Organization of fibrinous exudates between opposing serous surfaces results in adhesions. Utilization of

agents or methods that keep these surfaces apart or decrease the amount of fibrin present tends to prevent adhiscence and does not impede normal healing in areas operated on.

The fact that adhesions failed to appear in toxic or dying animals had been noted on several occasions. Tagnon and others have shown that fibrinolysis occurs in such cases and that if blood is taken in a test tube without an anticoagulant and allowed to clot it is observed that the clot disappears in a short time and becomes fluid again. Moreover, it cannot be clotted again by the addition of thrombin because the blood no longer contains fibrin. In Russia, during the war, it was found that blood taken from soldiers who died suddenly could be stored without the addition of an anticoagulant for the same reason.

In general, it is much easier to prevent partially the formation of adhesions between the parietal and visceral peritoneal layers than between contiguous visceral serosae. The principle of peritonealization of all raw surfaces and the avoidance of surgical trauma is obviously of critical importance. Careful eversion of incised peritoneal edges and the method of suturing employed to effect this is the corollary of this principle. Early ambulation and wound dressings that do not compress the abdominal wall to the operative areas are definite factors. Finally, the interposition of gases and poorly absorbed solutions between the viscera and the abdominal wall tends to decrease adhiscence between these layers.

To prevent the pathologic agglutination of the greater omentum to viscera with serosal injury is a far greater problem. The crucial consideration, however, seems to be the local concentration of fibrin, which as it clots forms the bridges through which fibroblasts permeate during the process of organization. The relative concentration of the other blood-clotting elements such as ionic calcium, thrombokinase, vitamin K and autogenous heparin and of prothrombin and thrombin, the precursors of fibrinogen and fibrin, is directly related to hepatic function and probably accounts for the variable tendency of adhesions to form in different subjects.

The introduction of the anticoagulants, especially heparin, intraperitoneally or systemically soon after serosal trauma diminishes the volume of fibrin in the exudate and so tends to limit the formation of local adhesions. For the same reason any adhesions that do form are more tenuous and elastic and therefore less likely to cause complications. The systemic use of anticoagulants for this purpose has been found to be more practical and more effective as well as less hazardous. Pitkin's menstruum and 20 per cent gelatin are good vehicles for heparin, although the former is considerably more irritating and painful locally.

The danger of hemorrhage, though real, should not be too great a deterrent, provided ordinary precautions are observed. Attention to hemostasis, postoperative coagulation and prothrombin times, as well as clinical observations of the pulse, blood pressure and blood counts, over a period of four to five days mitigates against this complication. The effect of heparin administered in short-acting vehicles for the first twenty-four hours is readily controllable. Excessive lowering of the clotting time is combated by transfusion, and Allen and others have shown that large doses of synthetic vitamin K intravenously are remedial against too great a reduction in plasma prothrombin. The action of dicumarol in experimental animals has been found much more difficult to control and the incidence of serious hemorrhage much more frequent than when heparin alone was employed. Furthermore, dicumarol is inferior to heparin as an antiadhesions agent.

## SUMMARY AND CONCLUSIONS

1. In part I of an experiment 37 dogs were subjected to one hundred and eight procedures in an attempt to control postoperative adhesions by transperitoneal or intraperitoneal operations and the following observations made: Early ambulation, careful peritonealization of raw surfaces, eversion of peritoneum by interrupted sutures in closures, avoidance of compressing wound dressings, pneumoperitoneum and infusions of slowly absorbed solutions such as gelatin were all partly effective in reducing the incidence of visceroparietal adhesions, despite the fact that viscerovisceral adhiscence recurred 100 per cent and more.

To combat the latter, infusions of heparin in isotonic sodium chloride solution, in 20 per cent gelatin and in Pitkin's menstruum were employed, and a reduction of from 50 to 75 per cent was obtained. In these experiments, best results were secured with 20 per cent gelatin as a vehicle. This decrement affected both visceroparietal and viscerovisceral adhesions. The chief complication was intraperitoneal bleeding, but this was largely self compensatory by absorption in practically all cases, the hemoglobin content returning to within 10 per cent of normal by the fourth day postoperatively. The least amount of bleeding occurred when gelatin was used as a menstruum.

2. In part II heparin and dicumarol were given systemically alone and in combination in sixty-four experimental procedures, divided into four groups. In these cases areas of serosa were not only abraded but also denuded. The results were as follows:

Group 1 (heparin in Pitkin's vehicle), Visceroparietal adhesions occurred in only 12 per cent. Viscerovisceral adhesions occurred between abraded areas in less than 1 per cent and in denuded areas in only 56 per cent.

Group 2 (heparin in 20 per cent gelatin). Visceroparietal adhiscence was found in 12 per cent and viscerovisceral adhiscence between abraded areas in 12 per cent and in denuded areas in only 68 per cent.

Group 3 (dicumarol orally). Visceroparietal adhesions were seen in 37 per cent and viscerovisceral adhesions in 50 per cent (mostly in connection with denuded surfaces. Fatal hemorrhages occurred in 4 of 16 animals (25 per cent). This drug was exceedingly difficult to control in dosage and action.

Group 4 (dicumarol orally and heparin in Pitkin's base administered subcutaneously). Visceroparietal adhiscence was seen in 31 per cent and viscerovisceral adhiscence in 56 per cent. Fatal hemorrhage occurred in 2 animals (12 per cent).

Heparin administered systemically by the subcutaneous route is a practical, effective and relatively safe agent in reducing the incidence of postoperative adhesions in experimental animals. It is more effective when used this way than when infused intraperitoneally, because its duration of action is more constantly sustained. Heparin is more effective and controllable than dicumarol or dicumarol and heparin in combination when used in the manner described. The hazard of serious hemorrhage is much less as well. Its action may be enhanced by utilizing some of the measures described here.

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# EFFECT OF OXIDIZED CELLULOSE IN THE PROTECTION OF THE SUTURE LINE IN INTESTINAL ANASTOMOSES IN DOGS

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LEAKAGE from the suture line in intestinal anastomoses is a complication of the gravest nature. Since oxidized cellulose, an absorbable substance that can be left in the tissues, has been introduced into surgical practice, its value as a protective aid in intestinal anastomoses seemed worthy of investigation.

The literature on intestinal anastomoses has been extremely voluminous.[1] The fundamental work of Lembert [2] and Halsted,[3] insisting on the importance of the serosal and submucosal sutures, remains the basis of successful anastomoses of the bowel.

As revealed by a rather extensive search of the literature,[1] the use of materials in protection of the anastomotic suture line apparently has not been reported to any great extent. Freeman [4] suggested the use of omental grafts for this purpose; Fenton and Peet [5] reported on the use of omental grafts in intestinal anastomoses in dogs. Devine [6] presented a preliminary report in which he used peritoneal and split thickness grafts applied with fibrin fixation to the anastomotic suture line in dogs.

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The material with which this work was done was supplied free of charge by Parke, Davis and Company, Detroit.

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Kenyon and his associates [7] found that oxidation of cellulose in a closed chamber with nitrogen dioxide produced an absorbable material. Its physical and chemical properties, as well as its clinical applications, have been extensively investigated and reported in the literature.[8]

Burns [9] found that oxidized cellulose implanted in the various portions of the peritoneal cavity of dogs forms a brownish gelatinous mass which gradually decreases in size until complete absorption occurs. Dmytryk,[10] working with dogs whose peritoneum had been traumatized, found that the primary reaction of the tissues to oxidized cellulose was a fibroplastic proliferation, with the formation of adhesions between omentum and intestines. When the oxidized cellulose was applied immediately after the incidence of the trauma, the adhesions were finer and less numerous than in the controls.

In the healing of serosal wounds, Hertzler [11] stated that within a few minutes the angle between the apposed surfaces is filled with a clear structureless exudate in which fibrin bundles rapidly form. With the passage of time, these bundles form fibrous tissue, cells wandering between the interstices of the fibrin bundles without replacement of the latter.

With these observations in mind, the following experiments were set up to investigate the possibility of oxidized cellulose protecting the anastomotic suture line. Two series of experiments were performed.

In both series adult dogs of various sizes and both sexes were used. Preoperative medication with morphine sulfate was used in doses regulated by the size of the animals. Anesthesia was induced and maintained by the intravenous injection of pentobarbital sodium. Strict aseptic technic was used in all the procedures. The abdominal wall was shaved and treated with tincture of iodine prior to the incision of the skin.

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In series I the abdomen was opened by a right rectus incision. The rectus muscle was split, and the peritoneal cavity was entered. The ascending colon was identified and brought to the surface. The peritoneal cavity was protected by sterile sponges. After the colonic contents were stripped from the segment of bowel to be used, the colon was clamped by rubber-covered intestinal forceps. The colon was then transected at a point 8 to 10 cm. from the ileocecal junction and immediately anastomosed end to end with a continuous circular through-and-through suture of the bowel. In the controls the abdominal wall was then closed in layers without drainage. Cotton was used as suture material throughout. A collodion covering was placed over the skin sutures.

The experimental animals were subjected to an identical procedure, with the additional step of applying an eight-ply layer of oxidized cellulose to the anastomotic suture line. The oxidized cellulose was held in position by interrupted serosal sutures placed well away from the line of intestinal suture. Great care was exercised that the lumen of the bowel was not entered by these supporting sutures.

In series II the steps of opening the abdomen, isolating the colon and protecting the peritoneal cavity were identical with those in series I. The colonic contents were stripped from the portion of the bowel to be used; the bowel was clasped with rubber-covered intestinal forceps and was transected. The cut ends were then approximated by the insertion of a Maunsell mesenteric suture, followed by a through-and-through continuous mucosal suture. The serosa was approximated by a serosal suture of the Cushing type. The abdominal wall was closed in layers. Cotton was used throughout as the suture material.

In the experimental animals of series II an identical procedure was performed with this additional step: After the two layer anastomosis had been done, an eight-ply layer of oxidized cellulose was put about the anastomotic line and held in position by interrupted serosal sutures placed well away from the line of anastomosis, care being exercised that the lumen of the colon was not entered in placing these sutures. The abdominal wall was closed in layers as in the previous operations, and the skin incision protected with collodion. Cotton was used throughout as the suture material.

After these described procedures, the animals were placed in cages and their progress observed daily. Water and food were allowed as tolerated, and no special animal diets were used.

## RESULTS

In series I, 3 dogs were used as controls. Two of these animals died, 1 at the end of twenty-four hours and the other at the end of forty-eight hours. One animal survived for ninety-six hours and was then killed.

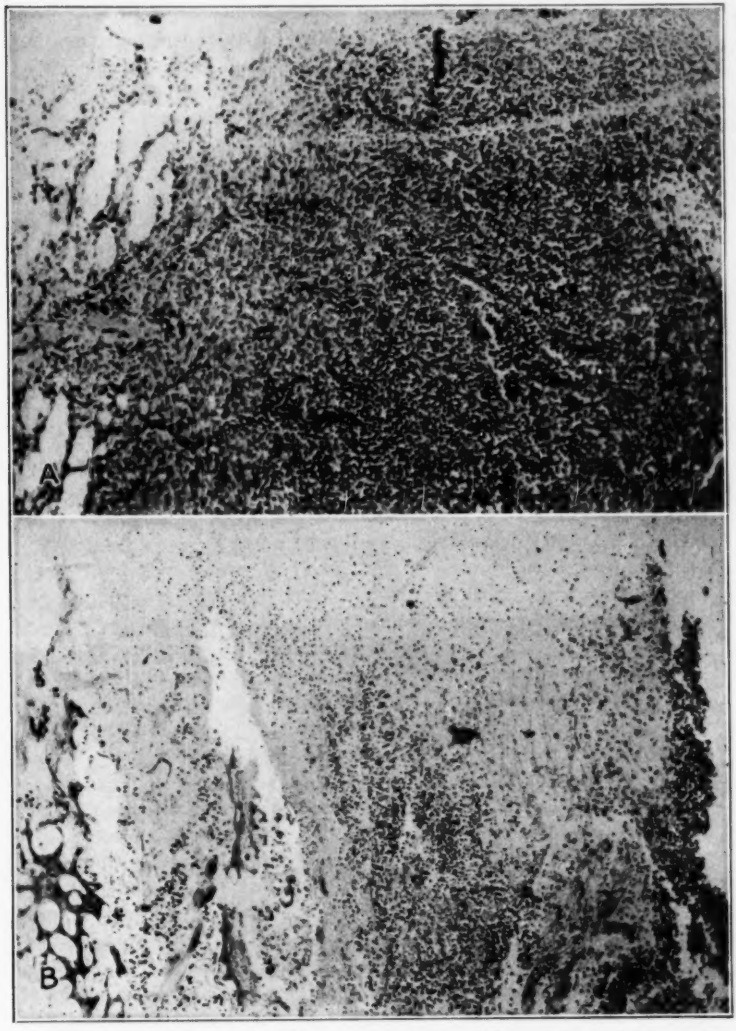


Fig. 1.—*A*, section of colon, showing acute inflammatory reaction with polymorphonuclear cell infiltration in serosal layer in a control animal in series I. Hematoxylin and eosin stain; × 100. *B*, section of colon showing acute inflammatory reaction in bowel wall. Fragments of oxidized cellulose in serosa of bowel with surrounding inflammatory exudate. Experimental animal in series I. Hematoxylin and eosin stain; × 100.

At autopsy the first 2 animals showed a generalized purulent peritonitis, with ileus. A large amount of free hemorrhagic exudate was found in the peritoneal cavity. The omentum was edematous and the colon gangrenous. No attempt at healing of the anastomotic line was evident, as there was free escape of colonic contents through the line of anastomosis. Histologically, a diffuse inflammatory exudate was present through the entire bowel wall, with gangrenous changes in the line of anastomosis. Much edema and many acute inflammatory cells were present in these sections. Few bacteria were noted in the exudate. Figure 1*A* is a photomicrograph showing these changes.

The animal killed at the end of ninety-six hours showed localized peritonitis, with many adhesions between the omentum, ileum and colon. No free fluid was found in the peritoneal cavity. There was little evidence of healing of the anastomotic line. Histologically, there was much serosal purulent exudate with a few clumps of bacteria. Early granulation tissue was present with a few foreign body giant cells about the cotton suture material. Much edema of the tissues was noted.

In the experimental group of series I the suture line was protected by an eight-ply layer of oxidized cellulose. Of this group, 3 animals died at the end of twenty-four hours, 1 died at the end of forty-eight hours and 1 lived five days.

Autopsy on the 4 animals that lived for twenty-four hours and forty-eight hours respectively showed acute purulent peritonitis with edema and gangrene of the colon. Much free hemorrhagic exudate was present. No healing of the line of anastomosis was present. Fecal material escaped from the lumen of the bowel between the sutured ends. In 3 of the animals no gross evidence of oxidized cellulose was found; in 1 animal that lived twenty-four hours postoperatively only a few scattered shreds of oxidized cellulose were found adherent to the serosal surface of the colon.

Histologically, a diffuse inflammatory exudate was seen throughout the bowel wall with a serofibrinous exudate on the serosa. Microscopic patches of oxidized cellulose were seen in which were many bacteria. More inflammatory cells were noted in the margins of the oxidized cellulose patches. Thrombi were present in many of the veins. Figure 1*B* is a photomicrograph showing the changes as described. Figure 2*A* is a higher power photomicrograph showing the particles of oxidized cellulose with the clumps of bacteria in and about the oxidized cellulose, with the acute inflammatory cells and hemorrhagic exudate. Figure 2*B* is a high power photograph of the bacteria and particles of oxidized cellulose.

Evisceration occurred in the animal surviving five days, and it was killed. There were many adhesions between colon, ileum and omentum, with localized peritonitis. Healing of the line of anastomosis was

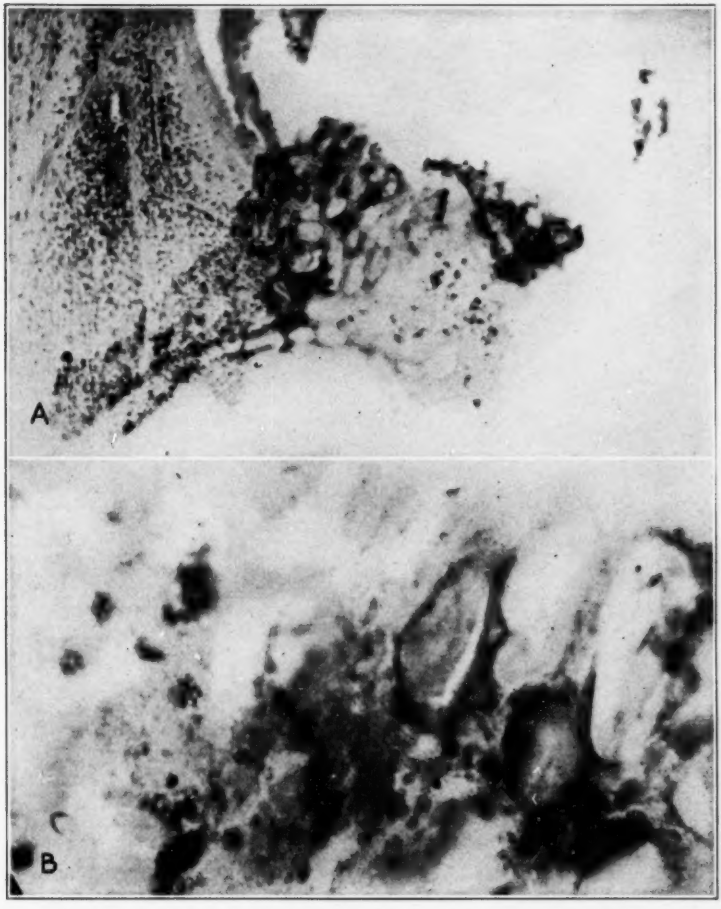


Fig. 2.—*A*, section of serosa under higher power showing oxidized cellulose fragments, hemorrhagic exudate and clumps of bacteria with acute inflammatory cell reaction. Experimental group, series I. Hematoxylin and eosin stain; × 250. *B*, section under high power showing hemorrhagic exudate, fragment of oxidized cellulose and clumps of bacteria. Hematoxylin and eosin stain; × 430.

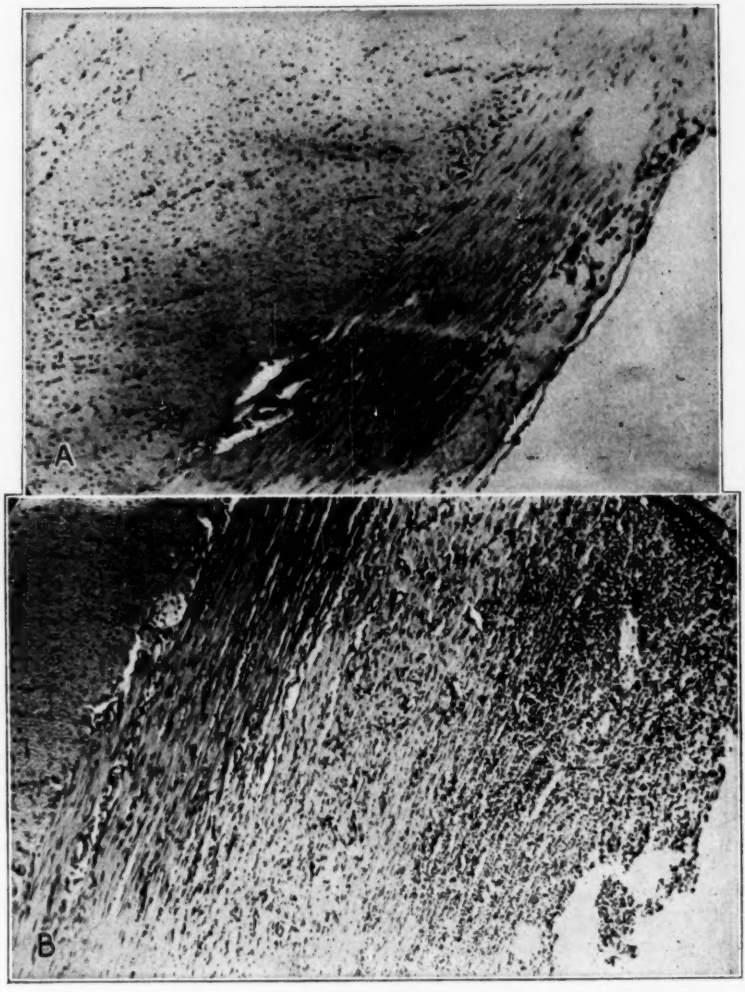


Fig. 3.—*A*, section of colon, showing clean serosa with chronic inflammatory cell reaction in the submucosa and fibroblastic reaction. Control animal in series II. Hematoxylin and eosin stain; × 100. *B*, section of colon showing acute inflammatory reaction in the serosa. Fibroblastic reaction and granulation tissue in the submucosa. Experimental animal in series II. × 100.

definitely delayed, as at autopsy the bowel separated easily at the site of anastomosis. No gross evidence of oxidized cellulose was found.

In series II, 3 of the 4 controls survived the operative procedure. Two were killed at the end of seven days and 1 at the end of nine days. At autopsy no peritonitis was present, and the lines of anastomosis were well healed. No adhesions of the intestines to the anterior abdominal wall were found. There were a few adhesions of the omentum, ileum and colon; no abscess formation was seen. The fourth animal died at the end of twenty-four hours; it did not regain consciousness after the operation. At autopsy there was no evidence of peritonitis, the peritoneum being clean and shiny. No free fluid was found in the peritoneal cavity. No leakage from the line of anastomosis was present.

Histologically, the serosa in these animals was clean; there was a small amount of hemorrhage, with a few chronic inflammatory cells near the point of suture. Granulation tissue with some acute and chronic inflammatory cells was seen. The serosa showed slight thickening. The line of suture was closed by young fibrous tissue with ingrowth of capillary vessels. Mitotic figures were seen in the fibroblastic tissue. Figure 3*A* is a photomicrograph illustrating the changes described in this paragraph.

The histologic examination in the animal dying in twenty-four hours showed acute and inflammatory cells in the wall of the bowel. No granulation tissue was present. The serosa of the bowel was clean.

Four animals were used in the experimental group, these animals having the suture line protected by an eight-ply layer of oxidized cellulose. All 4 survived the operative procedure. They were killed on the fifth, sixth, eighth and eleventh day postoperatively. At autopsy none of these animals showed generalized peritonitis. All of them had many firm, dense adhesions between the omentum, the ileum and the colon. In the middle of the mass of adhesions in all the animals was found an abscess filled with purulent material. No evidence of oxidized cellulose was found in any of them.

Histologically, a thick layer of purulent exudate was seen on the serosal layer of the colon, infiltrated with many acute inflammatory cells. In the deeper layers were capillary vessels and young fibroblasts showing mitotic figures. Occasional small abscesses were found in the submucosal layer of the bowel. Muscle was being replaced by fibrous tissue. A few giant cells were seen in the wall of the bowel. A few clumps of bacteria were seen in the exudate on the serosal layer of the bowel. Figure 3*B* is a photomicrograph showing the changes described here.

Tables 1 and 2 summarize the findings in the individual animals of both series.

TABLE 1.—*Results in Series I*

| Dog | Died | Results |
|---|---|---|
| | Control Animals | |
| 1 | 24 hr | Acute generalized peritonitis; gangrene of colon; free fluid in abdomen; ileus; no healing of anastomosis |
| 2 | 48 hr. | Acute peritonitis; free fluid in abdomen; ileus; gangrene of colon; no healing of anastomosis |
| 3 | 96 hr. (killed) | No healing of anastomosis; many adhesions between omentum, ileum and colon; localized peritonitis |
| | Experimental Animals (Oxidized Cellulose) | |
| 1 | 24 hr. | Purulent peritonitis, free fluid in abdomen and exudate on bowel; ileus; no healing of anastomosis, with leakage from suture site; 1 small piece of oxidized cellulose |
| 2 | 24 hr. | Purulent peritonitis, free fluid in abdomen and no healing of anastomosis, with leakage from suture line; no evidence of oxidized cellulose |
| 3 | 24 hr. | Same as in dog no. 2 |
| 4 | 48 hr. | Acute purulent peritonitis; free fluid and exudate in peritoneum; ileus; no evidence of healing of anastomosis, with leakage from the line of anastomosis; no evidence of oxidized cellulose |
| 5 | 5 days | Eviscerated; many adhesions between omentum, ileum and colon; no definite healing of anastomosis, localized peritonitis; no evidence of oxidized cellulose |

TABLE 2.—*Results in Series II*

| Dog | Survival | Result |
|---|---|---|
| | Control Animals | |
| 1 | 24 hr. | No peritonitis; no free fluid in abdomen; serosa smooth and shiny, no exudate no leakage from anastomotic site; death probably due to anesthetic |
| 2 | 6 days (killed) | No peritonitis; no adhesions to anterior abdominal wall; adhesions between omentum, ileum and colon; no abscess cavity; anastomosis well healed |
| 3 | 6 days (killed) | No peritonitis; anastomosis well healed; omentum attached to lateral side of colon; no adhesions between ileum and colon; no abscess |
| 4 | 9 days (killed) | No peritonitis; few omental adhesions; colon anastomosis secure and well healed; no adhesions between ileum and colon; no abscess formation |
| | Experimental Animals (Oxidized Cellulose) | |
| 1 | 5 days (killed) | No generalized peritonitis; many adhesions between omentum, ileum and colon; no evidence of oxidized cellulose; abscess in middle of mass of adhesions |
| 2 | 6 days (killed) | No generalized peritonitis; adhesions between omentum, ileum and colon; no evidence of oxidized cellulose; abscess cavity in middle of mass of adhesions |
| 3 | 8 days (killed) | No generalized peritonitis; adhesions between omentum, ileum and colon; no evidence of oxidized cellulose; abscess cavity in middle of mass of adhesions |
| 4 | 11 days (killed) | No generalized peritonitis; adhesions between omentum, ileum and colon; no evidence of oxidized cellulose; abscess cavity in middle of mass of adhesions |

COMMENT

The animals of series I were admittedly subjected to an extreme experiment to determine if oxidized cellulose would seal the suture line till healing or at least agglutination of the anastomosed ends of the bowel had taken place. Since Burns [9] found that oxidized cellulose early formed a gelatinous mass, the hope was entertained that this material might serve as an agglutinating factor to seal the ends of the bowel and thus prevent leakage of the intestinal contents. This hope was not realized, since 4 of the 5 animals of the experimental group did not survive the operation for a longer period than did the controls. It was further found that oxidized cellulose grossly disappeared much more rapidly from the infected peritoneal cavity than in the animals of Burns's [9] uninfected group. This disappearance may be due to the fluid concentration and the changes in hydrogen ion concentration reported to be present in the early phases of the infection. The disappearance of so large an amount of foreign material in so short a time apparently is not due to the action of the phagocytes. However, the cause of the rapid disappearance was not investigated at this time. It was further observed in microscopic sections that bits of oxidized cellulose appeared to induce a greater tissue reaction of inflammatory cells than occurred in the controls. Furthermore, clumps of bacteria were noted about and within the particles of oxidized cellulose; the latter may well serve as a nidus for the growth of pathogenic intestinal bacteria.

No conclusions can be drawn from the fact that 1 animal of the control group and 1 in the experimental group in series I did not succumb as early as did the other animals of this series. The matter of individual resistance to the spread of peritonitis plays a factor in either death or survival. It seems that such a factor protected these animals, since they were subjected to the same procedure as were the other animals.

In series II the experimental animals presented many more intraperitoneal adhesions than did the controls, which confirmed Dmytryk's [10] observation that oxidized cellulose will not prevent adhesions. In fact, from the results in these animals one may conclude that formation of adhesions is enhanced by the presence of this material. From the observations in the first series one can conclude that the additional inflammatory reaction induced by the oxidized cellulose will result in increased adhesions in the peritoneal cavity.

The finding of an abscess within the mass of adhesions in all the experimental animals of series II in which oxidized cellulose had been used was entirely unexpected. The explanation of this happening seems to be the fact that oxidized cellulose was placed in a potentially

infected field. Conditions favorable to bacterial growth such as warmth, fluid concentration and the presence of a soluble form of cellulose were met for the formation of an abscess. This theory is shown more plausible from observations in the first series, in which microscopic examination showed many clumps of bacteria in and about the particles of oxidized cellulose remaining on the serosa of the bowel.

## SUMMARY AND CONCLUSIONS

1. Oxidized cellulose did not prevent leakage from the anastomotic line in dogs when a single through-and-through suture end to end anastomosis was performed.

2. In the presence of infection in the peritoneal cavity of dogs, oxidized cellulose disappeared more rapidly.

3. Particles of oxidized cellulose appeared to promote the growth of bacteria in the infected peritoneal cavity of dogs.

4. In the presence of infection, oxidized cellulose appeared to induce increased formation of fibrous adhesions.

5. Abscess formation within the mass of adhesions formed when oxidized cellulose was placed in the potentially infected peritoneal cavity occurred in all the experimental animals used in series II.

6. In the presence of a potential infection in an operative field within the peritoneal cavity, the use of oxidized cellulose seems to be hazardous.

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## CORRECTION

In the article entitled "Lymphosarcoma of the Duodenum: Report of a Case; Review of the Literature," by Dr. Murray M. Copeland and Dr. D. James Greiner, which was published in the April 1949 issue of the ARCHIVES, the sidehead "Histopathologic Fracture" on page 524, line 8, should read "Histopathologic Features."

# INCREASE OF SERUM LIPASE IN EXPERIMENTALLY INDUCED APPENDICAL PERITONITIS

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THE USE of determinations of serum amylase and serum lipase in the diagnosis of diseases involving the pancreas has achieved great prominence during the past ten years.[1] Increases of serum amylase have been reported in cases of acute pancreatitis,[2] perforation of peptic ulcer into or near the pancreas [3] and trauma to the pancreas.[4] High

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From the Harrison Department of Surgical Research, School of Medicine, and the Graduate School of Medicine, University of Pennsylvania.

1. Bockus, H. L., and others: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1946, vol. 3, pp. 745-750.

2. (*a*) Chisholm, T. C., and Seibel, R. E.: Acute Pancreatitis: II. An Experimental Study with Special Reference to X-Ray Therapy, Surg., Gynec. & Obst. **85**:794, 1947. (*b*) Comfort, M. W., and Osterberg, A. E.: Serum Amylase and Serum Lipase in the Diagnosis of Diseases of the Pancreas, M. Clin. North America **24**:1137, 1940. (*c*) Appelbaum, I. L.: Serum Amylase in Mumps, Ann. Int. Med. **21**:35, 1944. (*d*) Lewison, E. F.: The Clinical Value of the Serum Amylase Test, Surg., Gynec. & Obst. **72**:202, 1941. (*e*) Somogyi, M.: Diastatic Activity of Human Blood, Arch. Int. Med. **67**:665 (March) 1941. (*f*) Heifetz, C. G.; Probstein, J. G., and Gray, S. H.: Clinical Studies on Blood Diastase: II. Significance of Increase of Blood Diastase, ibid. **67**:819 (April) 1941. (*g*) Sorkin, S. Z.: Blood Amylase Activity in Diseases of Carbohydrate Metabolism and in Non-Diabetic Pancreatic Disease, J. Clin. Investigation **22**:329, 1943.

3. (*a*) Probstein, J. G.: Perforated Peptic Ulcer: Its Differentiation from an Acute Pancreatitis by Blood Diastase Determination, J. Lab. & Clin. Med. **24**:449, 1938. (*b*) Myer, K. A., and Amtman, L.: Urinary Diastase Test in Peptic Ulcer Penetrating Into Pancreas, Am. J. Surg. **33**:307, 1936. (*c*) Comfort and Osterberg.[2b] (*d*) Lewison.[2d] (*e*) Heifetz, Probstein and Gray.[2f]

4. (*a*) McCaughan, J. M.: The Value of Estimations of the Amylase of the Blood in Diagnosis of Suspected Pancreatic Disease, Surg., Gynec. & Obst. **59**:598, 1934. (*b*) de Takats, G., and Nathanson, I. T.: Correlations of Internal and External Pancreatic Secretion; Effect of Ligation of Tail of Pancreas on Diastase in Blood, Arch. Surg. **19**:788 (Nov.) 1929. (*c*) Naffziger, H. C., and McCorkle, H. J.: Recognition and Management of Acute Trauma to Pancreas, with Particular Reference to Use of Serum Amylase Test, Ann. Surg. **118**:594, 1943. (*d*) Nemir, P.; Hawthorne, H. R., and Lecrone, B. L.: Unpublished Data.

transient increases have been obtained experimentally in cases of complete obstruction of the pancreatic ducts,[5] and a continued increase for over a year following permanent closure of the ducts has been reported.[6] Hyperamylasemia has also been observed in diseases of the salivary glands such as mumps,[7] although here also some investigators have ascribed the increase to transient pancreatitis.[8] The mass of evidence at hand,[7b,c] however, would indicate that the high amylase level in cases of mumps occurs most frequently without evidence of involvement of the pancreas.

The appearance of hyperamylasemia is explained on the basis of retrograde passage of the enzyme into the blood and lymph either through mechanical obstruction of the pancreatic duct (or parotid duct in cases of mumps [9]) or through the liberation of the enzyme as a result of acute damage or destruction of the parenchymatous cells which form the enzyme.[8a]

Decreased values for serum amylase have been obtained in cases of increased thyroid activity [10] and of impaired hepatic function.[11] It is felt [10a] that the decrease found in hyperthyroidism reflects an impairment of hepatic function. Decreased values have also been reported in distur-

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5. Zucher, T. F.; Newberger, P. G., and Berg, B. N.: The Amylase of Serum in Relation to Functional States of the Pancreas, Am. J. Physiol. **102**:209, 1932. Popper, H. L., and Sorter, H. H.: Blood Enzymes After Ligation of All Pancreatic Ducts, Proc. Soc. Exper. Biol. & Med. **48**:384, 1941. McCaughan.[4a] de Takats.[4b] Nemir, Hawthorne and Lecrone.[4d]

6. Golden, L. A.; Sieracki, L. A.; Handelsman, M. B., and Pratt, J. H.: Diastase Activity of Blood and Urine When the Pancreatic Ducts Are Permanently Closed, Am. J. Digest. Dis. **6**:327, 1939.

7. (*a*) Zelman, S.: Blood Diastase Values in Mumps and Mumps Pancreatitis, Am. J. M. Sc. **207**:461, 1944. (*b*) Candel, S., and Wheeloch, M. D.: Serum Amylase and Serum Lipase in Mumps, Ann. Int. Med. **25**:88, 1946. (*c*) Wolman, I. J.; Evans, B.; Lesber, S., and Jaegge, K.: Amylase Levels During Mumps: The Findings in Blood and Saliva, Am. J. M. Sc. **213**:477, 1947. (*d*) Dunlop, G. A.: The Diastatic Index in Acute Parotitis, Lancet **2**:183, 1933. (*e*) Appelbaum.[2c] (*f*) Lewison.[2d]

8. (*a*) Bodansky, M., and Bodansky, O.: Biochemistry of Disease, New York, The MacMillan Company, 1940, p. 277. (*b*) Fennel, E.: Amylase Determinations, Am. J. Clin. Path. **14**:89, 1944.

9. Somogyi.[2e] Candel and Wheeloch.[7b] Wolman and others.[7c]

10. (*a*) Bartlett, W.: Effects upon Blood Amylase of Variations in Thyroid Activity, Proc. Soc. Exper. Biol. & Med. **37**:843, 1937. (*b*) Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Clinical Studies on Blood Diastase, Arch. Int. Med. **67**:805 (April) 1941. (*c*) Comfort and Osterberg.[2b]

11. (*a*) Rachmilewitz, M.: Blood Diastase in Hepatic and Biliary Disease, Am. J. Digest. Dis. **5**:184, 1938. (*b*) Cajori, F. A., and Vars, H. M.: The Effect of Chloroform Anesthesia on Serum Amylase and Liver Esterase, Am. J. Physiol. **124**:149, 1938. (*c*) Lewison.[2d] Somogyi.[2e] Probstein.[3a] Gray, Probstein and Heifetz.[10b]

bances of carbohydrate metabolism,[10b] although Sorkin [2g] noted no change in 56 cases of diabetes mellitus.

Increases of serum lipase are felt to be a more accurate index of the involvement of the pancreas in disease.[1] Hyperlipasemia has been reported in cases of acute pancreatitis,[12] carcinoma of the pancreas,[13] cholelithiasis with jaundice,[14] and chronic pancreatitis.[15] Increased values have also been observed in cases of peptic ulcer perforating into the pancreas [2b] and in cases of pancreatic cyst.[16] They have been obtained experimentally after trauma to the pancreas or obstruction of the major pancreatic ducts.[17] Although high serum lipase levels have been reported in certain conditions in which involvement of the pancreas cannot be definitely incriminated, such as mumps,[7b] severe destruction of hepatic parenchyma [12b] and intestinal obstruction,[18] Johnson and Bockus [12c] have emphasized the specificity of the serum lipase levels in diseases involving the pancreas and have stressed the value of serial determinations.

During the course of some experiments on the role of the pancreatic enzymes in intestinal obstruction, we became interested in alterations of the serum lipase in cases of peritonitis, and we were stimulated to study the serum lipase in dogs with induced severe appendical peritonitis. The hyperlipasemia was detected by means of serial determinations.

Serial determinations of serum amylase were also made, and while no significant concomitant increase of amylase occurred, interesting findings developed which would add further evidence of the hepatic origin of this enzyme, and these findings will be the basis for a subsequent report.

## MATERIAL AND METHODS

The saccharogenic method for determining serum amylase, as outlined by Somogyi [19] and recommended as being the most accurate of the

12. (*a*) Baxter, H.; Baxter, S. G., and McIntosh, J. F.: Variations in Level of Serum Lipase in Experimental Pancreatitis, Am. J. Digest. Dis. **5**:423, 1938. (*b*) Johnson, T. A., and Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, Arch. Int. Med. **66**:62 (July) 1940; (*c*) Present Status of Serum Lipase Test, Am. J. Digest. Dis. **10**:1, 1943. (*d*) Comfort and Osterberg.[2b]

13. Comfort and Osterberg.[2b] Johnson and Bockus.[12b,c]

14. Comfort and Osterberg.[2b] Johnson and Bockus.[12b]

15. Comfort and Osterberg.[2b] Johnson and Bockus.[12c]

16. Johnson, T. A., and Lee, W. E.: Symposium on New Trends in Surgery: Pancreatic Cyst; Report of Five Cases, S. Clin. North America **22**:1677 (Dec.) 1942.

17. Cherry, I. S., and Crandel, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, Am. J. Physiol. **100**:266, 1932. Nemir, Hawthorne and Lecrone.[4d]

18. Nemir, Hawthorne and Lecrone.[4d] Johnson and Bockus.[12b]

19. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399, 1938.

available methods by Dozzi,[20] was employed in this study. Dog serum has twenty to twenty-five times the amylase activity of human serum,[21] which necessitated the use of smaller amounts of serum. The presence of amylase was detected with the use of cornstarch as the substrate. One cubic centimeter of serum was added to 5.0 cc. of a 1.5 per cent starch solution plus 2.0 cc. of sodium chloride buffer and incubated at 37 C. for thirty-five minutes. Reducing sugar formed from the starch digestion was determined by the colorimetric method of Folin and Wu [22] using 0.1 or 0.2 cc. of the filtrate for the determination. The amount of amylase in the blood is expressed in terms of milligrams of dextrose formed from the hydrolysis of starch solution by 100 cc. of serum.

The Lovenhart modification of the method of Cherry and Crandel [17] was used for the determinations of serum lipase. The amount of lipase in the blood is expressed in terms of cubic centimeters of 0.05 normal sodium hydroxide required to neutralize the fatty acids liberated by the action of 1.0 cc. of serum on an olive oil emulsion.[23] In the majority of cases determinations were run in duplicate. We have done over four hundred determinations of lipase in serum, duodenal contents and pure pancreatic juice and have been impressed with the consistency of the results. In a number of the animals operated on the specific gravity of the blood and plasma,[24] blood urea nitrogen [25] and blood chlorides [26] were determined.

Both normal animals and those operated on were placed on a standard diet of water and purina® dog biscuits for twelve to twenty-four hours before the blood samples were taken, and the dogs which were operated on were starved for twenty-four hours before operation. The blood samples were rapidly withdrawn from the femoral artery into a dry, sterile syringe, and the serum was immediately removed after the sample was centrifuged at 2,500 revolutions per minute for fifteen minutes.

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20. Dozzi, D. L.: An Evaluation of Methods for Determining Blood and Urinary Amylase, J. Lab. & Clin. Med. **25**:1303, 1940.

21. Reid, F.; Quigley, J. P., and Myers, V.: Studies on Animal Disastases: V. Blood and Tissue Diastases, with Special Reference to the Depancreatized Dog, J. Biol. Chem. **99**:615, 1932. Somogyi.[20] Cajori and Vars.[11b]

22. Folin, O., and Wu, H.: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

23. The olive oil emulsion used in all cases was prepared for us by L. B. Longaker, Inc., Philadelphia.

24. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625, 1926.

25. Karr, W. G.: A Method for Determination of Blood Urea Nitrogen, J. Lab. & Clin. Med. **9**:329, 1924.

26. Wilson, D. W., and Ball, E. G.: A Study of the Estimation of Chloride in Blood and Serum, J. Biol. Chem. **79**:221, 1928.

Every effort was made to obviate hemolysis as a source of error in the determinations. The samples were taken usually between 8 and 11 o'clock in the morning and were immediately analyzed. Eighty determinations of serum amylase and ninety-two determinations of serum lipase have been made on 46 and 51 normal dogs, respectively, prepared in this fashion.

In the experiments on animals with peritonitis 14 mongrel adult dogs weighing between 7.0 and 13.0 Kg. were used. Control determinations were taken the day before and the morning of operation. During the operations pentobarbital sodium (24.0 mg. per kilogram) was employed, and aseptic technic was used throughout. The abdomen was opened through a low right rectus incision and closed in three layers with silk. Peritonitis was induced in one of two ways. In 11 of the animals, subsequently referred to as group I, fulminating peritonitis was created by ligating and slitting the appendix after the method of Zintel, Wiley, Nichols and Rhoads.[27] as recommended by Harvey, Meleney and Rennie.[28] In 3 of the animals, subsequently referred to as group II, peritonitis was created by ligation of the appendix alone after the method of Fauley and his group[29] and Kay and Lockwood,[30] modified in that all the omentum distal to the spleen was removed at operation. Five of the 14 animals survived for ten days or longer (dogs 71, 69 and 1385 in group I and dogs 125 and 1398 in group II). This report is primarily concerned with these 5 animals. The remaining 8 dogs in group I all died of fulminating peritonitis between twelve and thirty-two hours after operation, with an average survival time of twenty hours. The remaining animal in group II also died of fulminating peritonitis between ninety-six and one hundred and four hours after operation. In addition to the water and dog biscuits allowed postoperatively, 4 of the 5 surviving animals received isotonic sodium chloride solution intravenously (40.0 to 100 cc. per kilogram every twenty-four hours) and penicillin-in-oil (150,000 units every twelve hours) for the first twenty-four to forty-eight hours, at which time these extra measures were discontinued. Dog 69, the fifth animal, received no treatment other than the standard diet. Generalized peritonitis was manifested in

27. Zintel, H. A.; Wiley, M.; Nichols, A., and Rhoads, J. E.: The Use of Streptomycin in Surgical Patients, Surgery **21**:175, 1947.

28. Harvey, H. D.; Meleney, F. L., and Rennie, J. W. R.: Peritonitis: III. Studies in Peritoneal Protection with Particular Reference to Action of Sulfonamides in Experimental Peritonitis, Surgery **11**:244, 1942.

29. Fauley, G. B.; Duggan, T. L.; Stormont, R. T., and Pfeiffer, C. C.: The Use of Penicillin in the Treatment of Peritonitis, J. A. M. A. **126**:1132 (Dec. 30) 1944.

30. Kay, J. H., and Lockwood, J. S.: Experimental Appendical Peritonitis, Surgery **20**:56, 1946.

all cases by the clinical course (abdominal rigidity, increase in temperature and pulse, vomiting and shock of varying degree), by the aspiration of abundant bloody peritoneal fluid, by the development of a wound abscess and by postmortem examination (in 3 of the animals killed at varying intervals). With few exceptions blood samples were taken at twenty-four hour intervals, usually between 8 and 11 o'clock in the morning, and immediately analyzed. In some cases twelve hour samples were taken in addition to the twenty-four hour specimens. When twelve hour samples were withdrawn at night, the serum was removed and immediately placed in the icebox at 0 C. to be run early the following morning. We found little, if any, diminution of the enzymatic activity

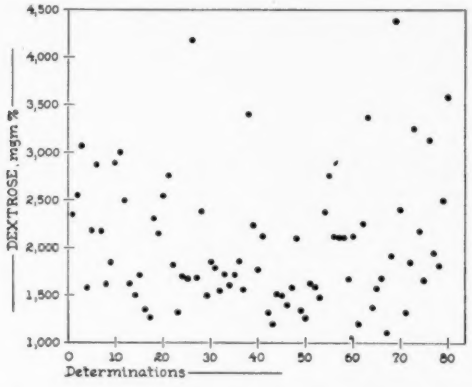


Fig. 1.—Results of eighty determinations of serum amylase on 46 normal dogs. The extreme range of variation is from 1,104 to 4,371 mg. per hundred cubic centimeters, with an average of 2,040 mg. Ninety-five per cent are in the range of 1,100 to 3,500 mg.

by this method provided the serum did not stand for longer than eight to twelve hours.[5]

## RESULTS AND COMMENT

The results of eighty determinations of serum amylase on 46 normal dogs are shown in figure 1. The values ranged from 1,104 to 4,371 mg. per hundred cubic centimeters, with an average of 2,040 mg. Seventy-seven (95.5 per cent) were in the range of 1,100 to 3,500 mg. While this great variation was evident among the different animals, it was not so marked when daily determinations were done on the same animal (fig. 2). It was noted, however, that rather pronounced variations within the normal range occurred in the same animal if blood samples were taken at various periods of the day despite the fact that the dog

was always on the standard diet. Friedman and Thompson [31] have noted also striking spontaneous increases of serum amylase in normal dogs.

The results of ninety-two determinations of serum lipase on 51 normal dogs are shown in figure 3. Serum lipase values in the normal dog are known to be low,[32] and this is borne out in our studies. In only three determinations were the values 1.0 cc. or over, and two of these (2.12 and 2.50 cc.) were in the same animal on successive days. In 95 per cent of the determinations the values were below 0.7 cc. The average for all the determinations was 0.29 cc. Daily determinations for six to ten day periods in 3 normal dogs showed a great constancy of the results, and only infrequently were values of 0.6 cc. or over noted. Sodium pentobarbital anesthetic alone, when administered to normal dogs prepared in an identical manner, had no effect on the serum lipase. Not even in dogs in which we have ligated both pancreatic ducts have we noted values as high as those which Dozzi [33] has reported

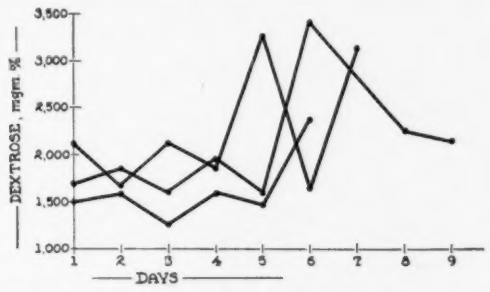


Fig. 2.—Serial determinations of serum amylase on 3 normal animals.

in 1 of his normal dogs (no. 411). We feel that values over 1.0 cc. represent a definite increase in the dog.

The results of daily determinations of serum lipase in the 5 dogs surviving fulminating peritonitis are shown in figure 4. Increases of over 1.0 cc. occurred in 4 of the 5 animals. It will be noted that the maximum increases occurred between the fourth and fifth days in the group I dogs and between the sixth and eighth days in the group II dogs. This will be referred to subsequently. It is possible that an increase above 1.0 cc. was missed in the remaining dog (no. 1385). This was

31. Friedman, I., and Thompson, W. R.: Induced and Spontaneous Changes in Blood Amylase, Particularly in Relation to Pancreas: An Experimental Study, Ann. Surg. **104**:388, 1936.

32. Baxter, Baxter and McIntosh.[12a] Cherry and Crandel. [17]

33. Dozzi, D. L.: Origin of Blood Amylase and Blood Lipase in the Dog, Arch. Int. Med. **68**:232 (Aug.) 1941.

one of the earlier dogs operated on in the series, and no samples were taken between the fourth and sixth days or after six days. On the basis of the occurrence in the other 2 dogs in this group, a rise might have been expected during the fourth to sixth days.

In view of the variations in serum amylase in serial determinations on normal dogs, we do not feel that any significance can be attached to the occasional slight and inconsistent rises noted in the surviving animals in which amylase levels were followed (fig. 5). However, the distinct and consistent decrease in the serum amylase within the first twelve to thirty-six hours after anesthesia and operation in all the animals has, we feel, considerable significance and has formed the basis for a subsequent report in preparation.

As Johnson and Bockus [12c] have stated, there are several explanations to account for increased lipase. Any mechanism which blocks one or more of the larger pancreatic ducts may cause an increase in the concen-

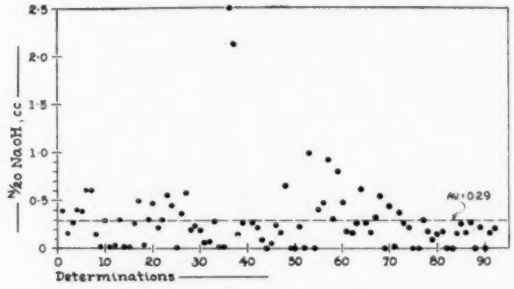


Fig. 3.—Results of ninety-two determinations of serum lipase in 51 normal dogs. Ninety-five and five-tenths per cent show levels below 0.7 cc., and in only three is the level 1.0 cc. or over. The average for all determinations is 0.29 cc.

tration of the serum lipase because of absorption of that ferment into the blood stream. Hyperlipasemia occurring in experimental ligation of one or more of the major pancreatic ducts, pressure of a tumor arising in or near the pancreas or edema of the pancreas or surrounding structures secondary to inflammatory changes would indicate this obstructive origin. A second method has been described as being the absorption of pancreatic debris secondary to an acute necrosis of the pancreas.

We feel that obstruction of the smaller ducts on the basis of an inflammatory edema is the method of production of the high lipase levels in the animals herein reported on. This has been indicated both by the serial lipase curves in the two groups of animals and by postmortem examination of the pancreas in 3 of the animals which were killed. It should be emphasized that every effort was made not to touch the

pancreas at the time of operation. We feel that trauma was not the mechanism of increase in any of these cases because after manipulative trauma to the pancreas the serum lipase rises in the first twenty-four to forty-eight hours.[34]

As noted (fig. 4), the maximum increase occurred after between four and five days in the animals in which the appendix had been

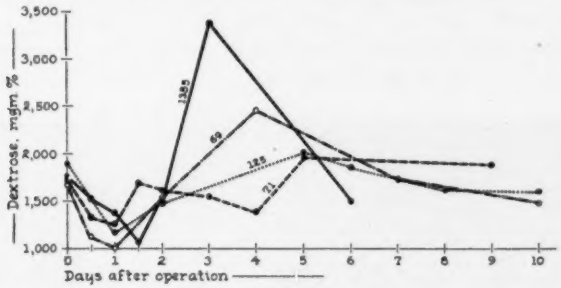


Fig. 4.—Results of serial determinations of serum lipase in 5 dogs surviving an induced, severe, fulminating appendical peritonitis for ten days or longer.

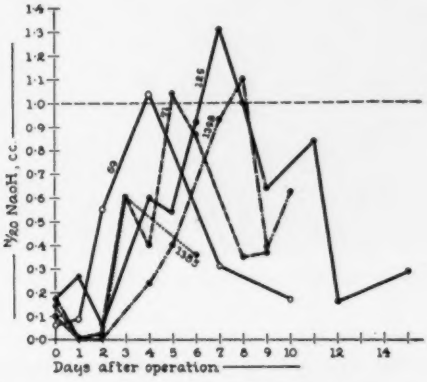


Fig. 5.—Results of serial determinations of serum amylase in 4 of the 5 animals surviving an induced, severe, fulminating appendical peritonitis for ten days or longer.

slit at operation. The onset of severe peritonitis was, therefore, immediate in this group. On the other hand, the maximum increases occurred in 6 to 8 days in the dogs in group II. Kay and Lockwood [30] have given a detailed analysis of the course of the animals operated on in

34. McCaughan.[48] Nemir, Hawthorne and Lecrone.[44] Cherry and Crandel.[17]

this fashion and have stated that the appendix has usually not ruptured by the second day. Therefore, in this group it is likely that the onset of diffuse peritonitis does not occur until some time between twenty-four and forty-eight hours after operation. If these conclusions be valid, then the length of time of the existence of diffuse peritonitis in relation to the time of maximum increase of the serum lipase becomes uniform in the two groups. This would indicate that, in the dog at least, it takes four to five days after the onset of severe, diffuse appendical peritonitis for the pancreatic function to be sufficiently impaired to result in hyperlipasemia.

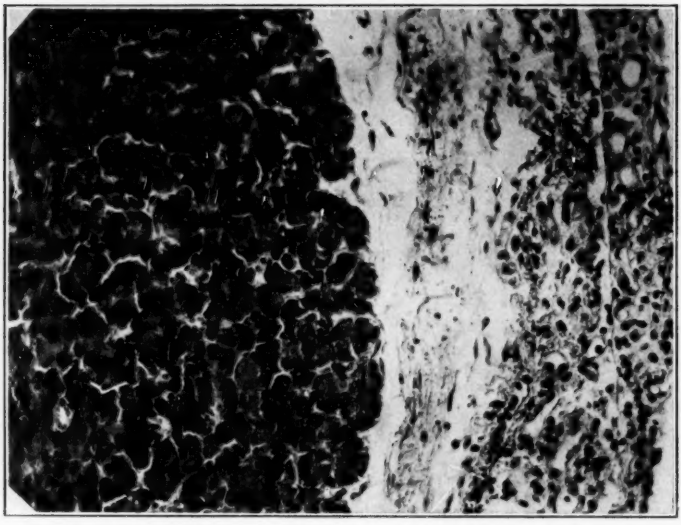

Fig. 6.—Section of right limb of pancreas of dog 125 showing peripancreatic inflammation; × 221.

Further positive evidence of the mechanism of production of the hyperlipasemia was afforded by postmortem examination. Two of the dogs (no. 69 and no. 1398) were killed at ten days and 1 (no. 125) at fifteen days after operation. The findings were similar in all 3 cases. Grossly, no changes were noted other than a dulness and thickening of the peritoneum overlying the pancreas. Examinations of sections from various portions of the gland showed similar changes in all. There was severe peripancreatitis with notable edema and infiltration of cells (fig. 6). Although polymorphonuclear leukocytes were present in abundance, the predominant cells were lymphocytes and

large mononuclear cells. This peripancreatic inflammation varied in severity in the different sections from the same gland, the right limb and body being affected much more than the left limb. In general, the cells of the gland were intact, but in dog 125 there was definite intralobular edema, and in dogs 69 and 1398 there was both interlobular and intralobular edema.

Examinations of the sections of pancreas from 3 of the animals dying between twelve and thirty-two hours after operation revealed uniformly a moderate interlobular and intralobular edema, but the peripancreatitis was minimal or absent entirely, the changes being directly related to the time of survival of the animal.

A recapitulation of the course of events would therefore seem to be as follows: Within twenty-four to thirty-six hours after the onset of diffuse appendical peritonitis, the pancreas became moderately edematous, but there was no active cellular infiltration around the capsule. By ninety to one hundred and twenty hours the generalized inflammatory reaction reached its maximum, and thickening, edema and infiltration about the pancreatic capsule had occurred. We feel that it is during this time that the pathologic processes combine to cause a blockage of the smaller pancreatic ducts, with a concomitant increase of the serum lipase. Subsidence of the inflammation then occurs; the lipase rapidly returns to normal, and chronic inflammatory cells come into prominence.

## SUMMARY AND CONCLUSIONS

1. Alterations in serum amylase and lipase in dogs having an experimentally induced severe, diffuse appendical peritonitis have been studied by means of serial determinations.

2. Of 14 animals operated on, 5 lived for ten days or longer, and 4 of these 5 demonstrated significant increases of the serum lipase. No significant concomitant increase of the serum amylase was noted in this series.

3. The maximum increase of serum lipase occurred in between four and six days after the onset of diffuse peritonitis, and the level rapidly returned to normal after the subsidence of the inflammatory reaction.

4. We feel that the mechanism of production of the hyperlipasemia is on the basis of peripancreatic inflammation and interlobular and intralobular edema, with resulting blockage of the smaller pancreatic ducts.

Dr. E. A. Case, of the Graduate School of Medicine, interpreted the histologic sections.

# SARCOMA OF THE ESOPHAGUS

## Report of Successful Resection of a Fibrosarcoma

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CHICAGO

PRIMARY sarcoma of the esophagus is a rare condition. Dvorak [1] in 1931 presented an excellent discussion of the entire subject and reviewed the reported cases up to that time. He found less than 50 cases in the literature, and in many of these there was considerable doubt concerning the exact pathologic process. Simon [2] three years earlier was able to collect only about 30 unquestioned cases.

Since 1931 there have been few additional cases of primary sarcoma of the esophagus reported. Jaleski and Waldo [3] described an interesting case of a primary melanotic sarcoma of the esophagus which was not diagnosed before autopsy. The tumor was polypoid, and there was extensive metastasis to the lungs, liver, pancreas, spine and regional lymph nodes. Cases of primary leiomyosarcoma of the esophagus have been contributed by Mallory,[4] Menne and Birge,[5] French and Garland [6] and Pennes.[7] Bayer [8] in 1941 reported on a patient with sarcoma of the esophagus free of symptoms fifteen months after roentgen ray therapy. The following case is presented because of the rarity of the condition and because no known successful resection of a primary sarcoma of the esophagus has been reported.

C. P., a white man aged 43, was admitted to the Oak Ridge Hospital on Feb. 22, 1947. About eight months before he had first noticed some difficulty in swallowing

From the Department of Surgery, University of Chicago.

1. Dvorak, H. J.: Sarcoma of the Esophagus, Arch. Surg. **22**:794 (May) 1931.

2. Simon, H.: Die Sarcome, Neue deutsche Chir. **43**:246, 1928.

3. Jaleski, T. C., and Waldo, P. V.: Primary Melanotic Sarcoma of the Esophagus, Am. J. Cancer **24**:340, 1935.

4. Leiomyosarcoma of Distal Third of Esophagus with Extension into and Ulceration of Mediastinal Lymph Nodes, Cabot Case 21501, New England J. Med. **213**:1194, 1935.

5. Menne, F. R., and Birge, R. F.: Primary Leiomysarcoma of Upper Third of Esophagus, Am. J. Digest. Dis. **3**:848, 1937.

6. French, L. R., and Garland, L. H.: Leiomyosarcoma of the Esophagus, Am. J. Roentgenol. **45**:27, 1941.

7. Pennes, A. E.: Leiomyosarcoma of the Esophagus, Am. J. Roentgenol. **48**: 336, 1942.

8. Bayer, L.: Ueber ein mit Röntgenstrahlen beseitigtes, seit 15 Monaten symptomfreies Sarkom de Speiseröhre, Monatschr. f. Krebsbekämpf. **9**:86, 1941.

solid foods. This dysphagia lasted about one month and then suddenly disappeared. For the next six months he was able to eat all kinds of food without any discomfort. One month before his admission he again began to have dysphagia, which rapidly progressed until he had difficulty even swallowing liquids. He became extremely weak and lost 30 pounds (13.6 Kg.) of weight. He never had a cough, but for several days prior to his admission his voice had been hoarse. The past history was noncontributory.

*Physical Examination.*—The patient appeared chronically ill, with obvious signs of recent loss of weight. There was no dyspnea. A definite hoarseness was noted. The lungs were clear. The heart rhythm was regular, and no murmurs could be heard. The blood pressure was 140 systolic and 90 diastolic and the pulse rate 70. The reflexes were equal and active.

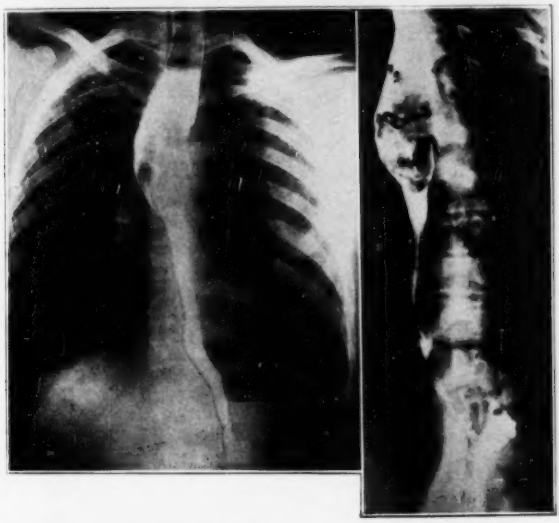

Fig. 1.—Roentgenograms of esophagus after ingestion of barium. Anterior and lateral views show a large filling defect in the upper region extending from the level of the clavicles to below the arch of the aorta. The esophagus in the region of the tumor has dilated, allowing barium to flow around the mass.

*Laboratory Data.*—All blood counts were within normal limits. The urine was normal, and the Wassermann reaction was strongly positive. Roentgenologic examination after the administration of barium revealed a large polypoid mass in the upper part of the esophagus which filled the entire lumen (fig. 1). The pulmonary fields were normal.

*Esophagoscopy.*—At 26 cm. from the upper incisors an irregular grayish brown firm mass was seen which filled the entire lumen of the esophagus. There was definite dilatation of the esophagus above the tumor. A biopsy was performed, which showed the lesion to be a fibrosarcoma.

*Preoperative Preparation.*—The patient received a high protein liquid diet supplemented with vitamins. In addition he was given one blood transfusion and

500 cc. of plasma. Large doses of penicillin were given in order to render the patient noninfective from a syphilitic standpoint.

*Operation.*—Cyclopropane, ether and oxygen anesthesia administered through an endotracheal tube was employed. The patient was placed on his right side and the left side of the chest opened through the bed of the sixth rib, which had been removed subperiosteally. The third, fourth, fifth and seventh ribs were transected posteriorly near their accompanying transverse processes and the intercostal structures between these ribs divided and ligated. A 2 cm. segment of the left phrenic nerve was excised in order to paralyze permanently

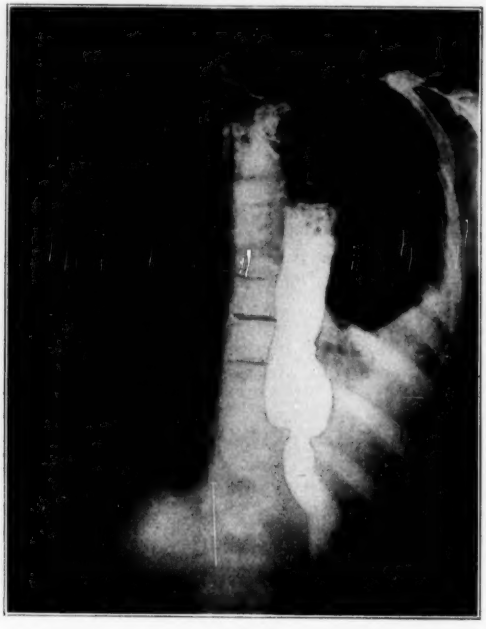

Fig. 2.—Roentgenogram of esophagus and stomach following ingestion of barium, fourteen days after resection and esophagogastrostomy. It shows all of the stomach in the thorax. The anastomosis is above the level of the clavicle, and the diaphragm is closed around the pylorus.

the left leaf of the diaphragm. Exploration of the mediastinum failed to reveal any evidence of metastasis. The esophagus was freed from the posterior mediastinum from just above the esophageal hiatus upward to the arch of the aorta. The vagus nerves were sacrificed. The lower portion of the tumor mass was located just below the arch of the aorta, and in order to facilitate mobilization of the esophagus in this region the mediastinal pleura was incised above the arch of the aorta and lateral to the left subclavian artery. By means of blunt dissection both above and below the arch of the aorta, the esophagus was readily freed from the adjacent mediastinal structure. A small firm node attached to the carina was removed.

The upper portion of the tumor extended into the base of the neck and necessitated freeing of the esophagus above the level of the sternal notch. The abdomen was now entered through a radial incision in the left side of the diaphragm. There was no gross evidence of metastasis. The spleen was removed. The upper four fifths of the stomach was mobilized by dividing the omentum distal to the gastro-epiploic vessels and the left gastric artery close to its origin from the celiac axis. The stomach was transected just below the cardioesophageal junction and the

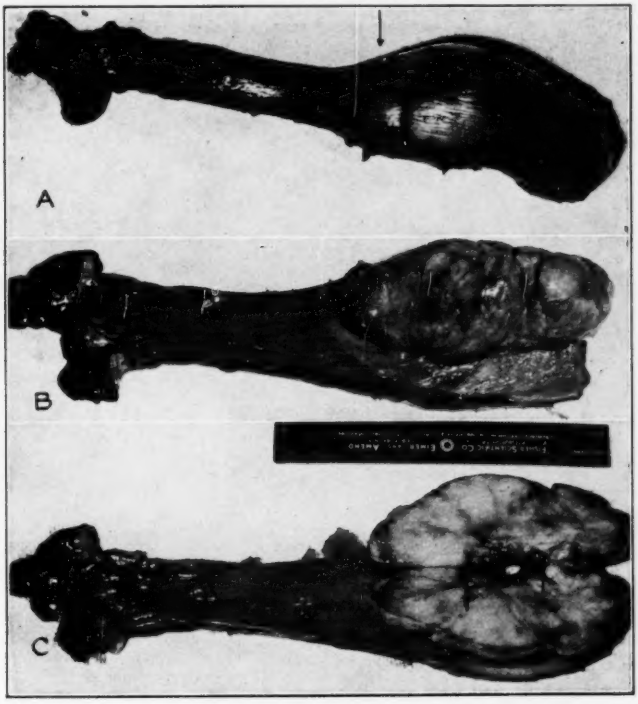


Fig. 3.—Photographs of the resected specimen of esophagus. *A* shows the marked dilatation of the upper region. The arrow points to depression caused by arch of aorta. *B* shows the esophagus open. Note large polypoid mass filling the entire lumen of the esophagus. Gastroesophageal junction is shown. *C* shows the polypoid mass cut through the center. Area between arrows shows pedicle of the tumor.

distal opening infolded. The mobilized esophagus was drawn out through the opening in the mediastinal pleura above and to the left of the arch of the aorta. The stomach was easily brought up to the base of the neck and an anastomosis made between the esophagus and an opening in the fundus of the stomach. The esophagus was transected 4 cm. above the upper limit of the tumor. In spite of the high position of the anastomosis there was no apparent tension on the suture

line. The diaphragm was closed about the pylorus, and the chest was closed tightly. A catheter was brought out through the ninth inner space for pleural drainage. The patient received 2,500 cc. of blood during the operation.

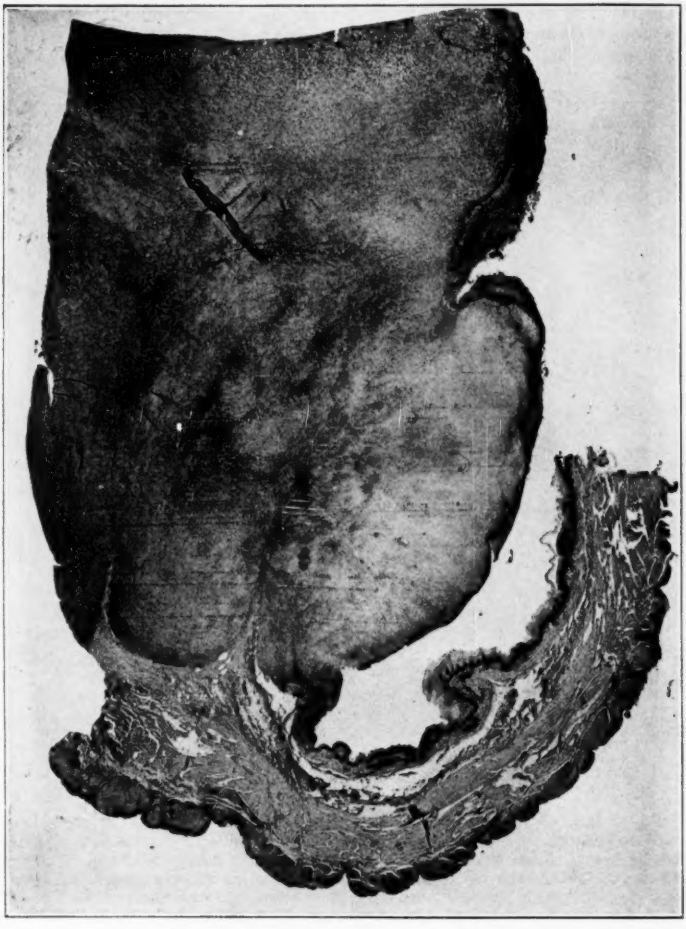

Fig. 4.—Photomicrograph in region of the pedicle of the tumor. The tumor is shown to be well circumscribed and is arising from the submucosa. There is no invasion into the muscularis.

*Postoperative Course.*—The patient had an uneventful convalescence. A stomach tube which had been placed at the time of operation was connected to a suction apparatus and negative pressure maintained for seventy-two hours. From the

third to the ninth day he was given small amounts of nourishing liquids every hour through this tube. On the ninth day the tube was removed and he was started on oral feedings, which he tolerated well. Antibiotics were given for ten days. Blood and plasma were administered as needed. He was up and walking about the ward on the seventh day and was discharged on the fourteenth postoperative day. Roentgenologic examination after a swallow of barium made two weeks postoperatively revealed the entire stomach in the thorax and a well functioning esophagogastrostomy opening. The site of anastomosis was above the level of the clavicles (fig. 2). He returned to work two weeks after his discharge from the hospital.

*Pathologic Report.*—Gross Examination: The specimen consisted of 28 cm. of esophagus. The upper 11 cm. was dilated and the lumen filled with a firm, elastic,

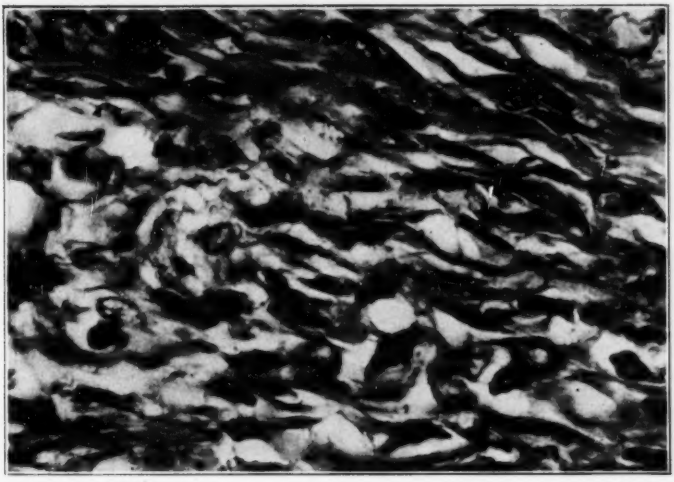

Fig. 5.—Photomicrograph showing the tumor to be composed of connective tissue cells. Myofibrils could not be demonstrated by phosphotungstic acid and hematoxylin stains.

bulbous growth. The open esophagus presented no noteworthy changes except for a tumor mass which measured 12 cm. in length and 4.5 cm. in diameter. The surface of the tumor was lobulated and grayish red with scattered areas of yellow. It was attached to the posterior wall of the esophagus by a pedicle measuring 4.5 cm. by 0.4 cm. (fig. 3). The cut surface was relatively uniform and presented a slightly moist, pale appearance with a grayish red tracery. There were occasional areas of softening.

Microscopic Examination: The tumor seemed to arise from the submucosal region and did not invade the muscularis. The surface of the growth was devoid of epithelium (fig. 4). The mass was composed of cells presenting the configurations of connective tissue cells. These cells varied in size, shape and staining properties. Some had large nuclei; others were vesicular, with prominent nucleoli. There was considerable hyperchromasia and a moderate number of mitotic figures. Phosphotungstic acid stains did not reveal any myofibrils (fig. 5).

## COMMENT

Sarcoma of the esophagus is clinically differentiated from carcinoma with difficulty. The symptoms of the two are similar. The age distribution and sex incidence are the same as that of carcinoma.

Sarcomas of the esophagus are usually divided into two general groups, the diffuse infiltrating type and the polypoid type. The former contain round or polyhedral cells and metastasize early, while the latter are usually composed of spindle cells and metastasize late.

In the case presented there was a history of progressive difficulty in swallowing which began eight months before the patient's admission to the hospital. The dysphagia lasted for about one month and then suddenly subsided. It is probable that a polypoid growth was present at that time which was similar to that found at the time of operation but because of the peristaltic movements of the esophagus and the pressure exerted by the ingested food the mass broke off, relieving the obstruction. During the ensuing six months the polypoid growth slowly recurred. In spite of the long history and the large size of the intraluminal growth there was no evidence of invasion through the wall of the esophagus. The node removed from the carina showed invasion with tumor cells and was the only evidence of metastasis found.

Although there is considerable disturbance of gastrointestinal physiology associated with esophagectomy, this patient had little difficulty after the operation. He was able to eat well, had the sensation of hunger and never experienced any regurgitation of gastric contents.

Preservation of an adequate blood supply to the esophagus and stomach is of prime importance in the successful outcome of high esophageal resections. Division of the esophagus should be high enough to reach the esophageal branches of the inferior thyroid artery. Mobilization of the stomach should be carried out so as to preserve the arcade of vessels on the greater and lesser curvatures.[9] If these arcades are preserved to supply adequately the intercommunicating vessels within the wall itself, the stomach can be mobilized down to the pylorus without any fear of necrosis.

## SUMMARY

A fibrosarcoma of the upper part of the esophagus was successfully resected. The esophagogastric continuity was reestablished by an anastomosis between the stomach and the esophagus over and above the arch of the aorta.

9. Clark, D. E.: Transthoracic Esophagogastrostomy for Carcinoma of the Middle Third of the Esophagus, Ann. Surg. **121**:65, 1945.

# NEW ADVANCES IN SEAMLESS PROSTHETIC HANDS

CARL D. CLARKE, Ph.D.
AND
FELIX WEINBERG
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IN A PREVIOUS article, "Seamless Prosthetic Hands: A Technic of Fabrication."[1] methods of producing prosthetic rubber and plastic hands in rubber molds were explained in detail. Since the appearance of this article, numerous advances have been made. They are primarily new methods of producing molds and improved plastics and a technic of making partial hands.

## ELEMENTARY CONSIDERATIONS

Nineteen years ago one of us (C. D. C.) produced seamless electroplated molds over actual amputated hands. Agar molds were also used to cast seamless wax hands, which were treated with graphite and electroplated. In any event, both methods produced difficulties. The actual dead hand could serve as a pattern only once. It was possible to get no more than one wax hand out of an agar mold. Suitable resilient plastics had not been discovered at that time. Therefore, rubber was the prosthetic material of choice. Even today some workers are making plastic impressions in sodium alginate composition molds. This material is similar to agar and also a derivative of kelp. It permits only one good impression in the plastic. The rubber mold as described in the previously mentioned article permits the making of fifteen good plastic hands before the mold deteriorates. In spite of this fact, the demand for prosthetic hands is so great that it has become necessary to return to the electroplated metal mold for quantity production. From a single such mold, hundreds of plastic positive prosthetic hands may be obtained.

These resilient resin casts or skinforms possess a wealth of surface detail, a lifelike luminosity with rubber-like resiliency and strength. They are also entirely devoid of the seam or join lines inevitable when

From the Plastic Artificial Eye and Restorations Research Laboratory, Veterans Administration, School of Medicine, University of Maryland.

1. Clarke, C. D.; Weinberg, F. B., and Blevins, G. C.: Seamless Prosthetic Hands: A Technic of Fabrication, Arch. Surg. **54**:491-516 (May) 1947.

two piece molds are employed. They make ideal models or patterns from which metal quantity molds may be made by electroforming. Unfortunately latex molds have a short productive life, since only about fifteen casts may be made from a single mold. Nevertheless, all fifteen can serve as patterns for electroplating or electroforming. The chief limitation of the latex mold lies in the disparity in the curing temperature of rubber latex and vinyl plastic. The temperature of 130 C. required to cure most of the vinyl resins would completely destroy a latex mold, since rubber resinifies or becomes syrupy at 125 C.

In order to overcome this difficulty, we remove the mold when the cast is partially cured, or "turned over" as expressed by the trade. That is, after it has been in the oven for forty-five minutes at 100 C. and is sufficiently strong to be separated without danger of tearing. The removed cast or skinform is then immersed in a glycerin bath at 130 C. for a final cure. This method is superior to raising the temperature slowly with the cast immersed, because of the danger of overheating and blistering the cast. On cooling, the completely cured cast is removed and the gylcerin washed off in running water. While the hand may be carefully removed from the hot glycerin with blunt instruments, the plastic skinform while hot is extremely friable and inadvertent handling or strain will cause it to fracture. The glycerin-cured cast will have a more lifelike appearance as well as greatly increased resistance to wear and tear. Skinforms prepared in such a manner are entirely satisfactory for making the actual hand prosthesis. However, because of the fact that only fifteen skinforms may be obtained from a single rubber mold, these are used as patterns for making metal molds capable of producing thousands of identical duplicates.

The problems of producing these electroplated molds over the plastic hands that were obtained from rubber molds were many. Most plastics are excellent electroinsulating materials. The hand must be made conductive to electricity. Graphite was applied with a brush, as is done in electrotyping. While excellent deposits could be obtained, the surface so treated would not conduct electricity. Bronze and brass lacquers were used, as is done on leather for making this material conductive to electricity. This method worked, but the thicker coats of lacquer powder mixture destroyed some of the surface detail of the plastic. It must be borne in mind that the plastic hand should have every pore detail in sharp relief. The cast must produce fingerprint patterns; otherwise the prosthesis suffers by comparison with a real hand. The bronze lacquer was discarded. It was then decided to attempt to produce a silver deposit on the pattern, as is used in silvering mirrors. Such deposits are electroconductive, and at the same time the deposit is so thin that none of the infinite details is lost.

### REPAIR OF VINYL PLASTICS

Before a plastic skinform is used for a pattern in electroplating, it must be correct in every detail. As a result of undue stress and strain while hot, the vinyl plastics are sometimes torn. If these tears are extensive, the hand is discarded. Small torn places may be repaired as follows: Particles of the cured vinyl plastic are put into a large-mouthed bottle of cyclohexanone and shaken from time to time until dissolved. This solution of cured vinyl acetate-chloride in cyclohexanone makes an excellent repair medium or cement. A small amount of this cement is brushed on the edges to be joined with a small camel hair brush. The edges are approximated and the surplus medium removed with a dry cloth. Drying should continue until the cyclohexanone is completely volatized.

### ESSENTIAL STEPS IN THE PROCESS

The formation of suitable metal molds involves a series of definite steps which are as follows:

1. Mechanically stiffening the flexible pattern with a wax support.
2. Attaching the cathode wires.
3. Cleaning the surface.
4. "Sensitizing" the surface.
5. Formation of the silver electroconducting film by chemical reduction.
6. Electroplating the surface.
7. Metal spraying the surface for thick build-ups.
8. Removing the pattern.
9. Applying the separating medium.
10. Making the plastic duplicate.

### MECHANICALLY STIFFENING THE PATTERN

A thin pattern must be chosen for the electroplating or metal-spraying process. Otherwise extreme difficulty will be experienced in removing the pattern from the final metal mold. The plastic or rubber hand on removal from a rubber or metal mold is soft and flexible. Such a pattern is not sufficiently rigid to stand alone. To prepare a metal mold from the skinform, it becomes necessary to make the hand temporarily rigid or stiff enough to stand, without bending, the pressure of air spraying in sensitizing, silvering and the general handling necessary during the first stages of electroplating. To accomplish this we simply pour the hand full of melted waxes, while lowering it into a vessel of cold water. The internal pressure of the wax against the pressure of the water on the external surface of the hand prevents it from becoming distorted. At the same time, the cold water sets the wax in an even deposit on the inner surfaces of the hand. A deposit of

about 3 mm. of wax is allowed to build up on the inner surface, and then the excess wax is poured back into the pot.

A fifty-fifty mixture of paraffin and B square microcrystalline wax [2] serves excellently for this purpose. The thickness of the deposit can be determined during the build-up by simply blowing the liquid wax away from an edge. The set or congealed wax remains and is distinguishable from the liquid wax. It is best not to pour the wax into the hand until it has cooled sufficiently to be handled without burning the fingers. Furthermore, under such conditions, the build-up takes place in less time. Extreme care must be taken to prevent the wax from overflowing to the outer or skin surface of the hand. If this happens details on the surface of the hand will be lost and the silver spray and electroplated deposits will not stick. If the deposit of wax is too thick or the hand is entirely solid with wax, it will float in the electroplating bath, making the plating difficult or impossible.

After wax of proper thickness is deposited within the hand, it is ready to receive the connectors between the electrode and the hand. These are made of heavy copper wire, attached to three battery clamps. One battery clamp is connected to the center of a 6 inch (15 cm.) piece of 8 gage copper wire. One clamp is then fixed to each end of the wire. These end clamps are attached to the plastic hand. All silver-spraying and metal-plating operations are now carried out while the hand is attached to the connectors.

### CLEANING THE SURFACE

The proper preparatory treatments of plastic surfaces are the governing factors which make for the success or failure of any process for "silvering" plastics. This "deglazing" or "degreasing" of the plastic surface, its cleaning and so-called "sensitizing" or making the surface more receptive to the conductive film to be formed thereon are important steps in the process which cannot be overlooked. Even fingerprint marks or grease marks must be washed away. Otherwise a nonadherent and mottled silver film may result.

It is a well known fact that sprayed or electroplated metal deposits do not readily stick to greasy surfaces. Plastic hands as obtained from rubber molds, while in the strictest sense not greasy, nevertheless must be treated with a degreasing agent before silver spraying. The areas between the fingers seem to be particularly susceptible to this nonsticking of the silver deposit, which invariably results in a failure of a uniform electrodeposit of metal. We found that the hands could be cleaned by scrubbing with a wet brush dipped in plaster of paris or better still washed with one of the detergents such as a fairly concen-

2. Bereco Oil Company, Tulsa, Okla.

trated solution of trisodium phosphate. These hands could be degreased with carbon tetrachloride. The latter method, while satisfactory, was more costly and troublesome. We finally used the trisodium phosphate for the degreasing process. The hands were simply dipped into the semiconcentrated solution and the surface scrubbed with a brush. Or they can be soaked in the solution for half an hour. The plastic pattern should be thoroughly rinsed in water to remove the cleaning agent. The next step in the process is carried out while the hand is still wet.

It is then necessary to sensitize the plastic to receive the silver spray. This is done with the following formula:

**Stannous chloride sensitizing solution:**

| | |
|---|---|
| Stannous chloride | 10 to 12 Gm. |
| Hydrochloric acid | 5 cc. |
| Distilled water | 395 cc. |
| Ethyl alcohol | 600 cc. |

The acid is added to the stannous chloride, then the water and finally the alcohol, and the mixture is well shaken. This mixture can be sprayed on the plastic hands, or the solution can be painted on with a brush.

Another satisfactory sensitizing solution is as follows (its disadvantages lie in its harassing effect):

**Formaldehyde sensitizing solution:**

| | |
|---|---|
| Formaldehyde | 250 cc. |
| Water | 4,000 cc. |

Weiss [3] suggested immersion for a half to one hour in a mixture made up of the following chemicals:

| | |
|---|---|
| Stannous sulfate | 25 to 40 Gm. |
| Sulfuric acid (66° Bé) | 5 to 20 cc. |
| Ethyl alcohol | 120 to 250 cc. |
| Quinol | 5 to 15 Gm. |
| Water | 600 to 1,000 cc. |

Walker [4] recommended a solution of the following composition:

| | |
|---|---|
| Stannous chloride | 360 Gm. |
| Hydrochloric acid (chemically pure) | 212 cc. |
| Water | 4,000 cc. |

Some prefer a more dilute stannous chloride solution represented by the following formula:

| | |
|---|---|
| Stannous chloride | 10 Gm. |
| Hydrochloric acid (chemically pure) | 40 cc. |
| Water | 1,000 cc. |

### FORMATION OF THE SILVER ELECTROCONDUCTIVE FILM

After the sensitizing, the hands are sprayed simultaneously with a silver solution and a reducing agent. This must be done through a dual nozzle spray gun.[5] The silver solution and reducing agent cannot be

3. U. S. patent 2,355,933 (Aug. 15, 1944).

4. U. S. patent 2,303,871 (Dec. 1, 1941).

5. Paasche Airbrush Company, 1909 Diversey Parkway, Chicago.

mixed until they meet on the plastic hand. The reducing agent converts the silver solution into a metallic silver deposit on the surface of the plastic.

We use the following reducing and silvering solutions:

Reducing solution:

| | |
|---|---|
| Hydrazine sulfate | 28.3 Gm. |
| Ammonium hydroxide | 10 to 15 cc. |
| Water | 4,000 cc. |

Twenty-five cubic centimeters of the water is added slowly to the hydrazine sulfate and ammonium hydroxide until they are in complete solution.

Silver Solution:

| | |
|---|---|
| Silver nitrate | 71 Gm. |
| Distilled water | 4,000 cc. |
| Ammonium hydroxide | Sufficient barely to redissolve the precipitate formed on adding the first portion of ammonium hydroxide (approximately 70 cc.) |

Three fourths of the water and the silver nitrate is stirred until it is in complete solution. The ammonium hydroxide is added slowly until the solution becomes opalescent in appearance. At this point the process is continued with care to prevent the addition of too much ammonia. The amount is approximately 70 cc. Then the rest of the water is added to the mixture. The Bureau of Standards Circular Number 389 (1931)[6] lists three methods for producing silver films or mirrors on glass. These methods work equally well on organic plastics. However, in commercial application, a modified formulation using formaldehyde (40 per cent) as the reducing agent is being employed, with excellent results.

Ammoniacal silver nitrate solution:

| | |
|---|---|
| Silver nitrate (chemically pure) | 60 Gm. |
| Distilled water | 1,000 cc. |
| Ammonium hydroxide (28 per cent) | 60 cc. |

Reducing solution:

| | |
|---|---|
| Formaldehyde (40 per cent by volume) | 65 cc. |
| Distilled water | 1,000 cc. |

Even a little too much ammonia will prevent the silver from building up a deposit on the plastic; too small an amount will bring about an undesirable excess of precipitated oxide.

The 60 Gm. of chemically pure silver nitrate is completely dissolved in the 1,000 cc. of water. When the concentrated ammonium hydroxide is added, the mixture should be stirred constantly. The precipitate which is formed at first will redissolve when the rest of the ammonium hydroxide is added. The resulting solution, after 60 cc. of concentrated ammonium hydroxide has been added, will contain the proper amount of free ammonia for a correct silvering solution. Only

6. United States Department of Commerce, Jan. 6, 1931.

concentrated ammonium hydroxide (28 per cent; specific gravity, 0.90) should be used in this formulation. If the strength of the ammonium hydroxide has decreased on standing, a proportionate amount more must be used in the formula.

The reducing solution is made by adding 65 cc. of formaldehyde (40 per cent by volume) to 1,000 cc. of distilled water. Here again, if the strength of the formaldehyde has lessened, a proportionate increase in the amount of formaldehyde must be employed.

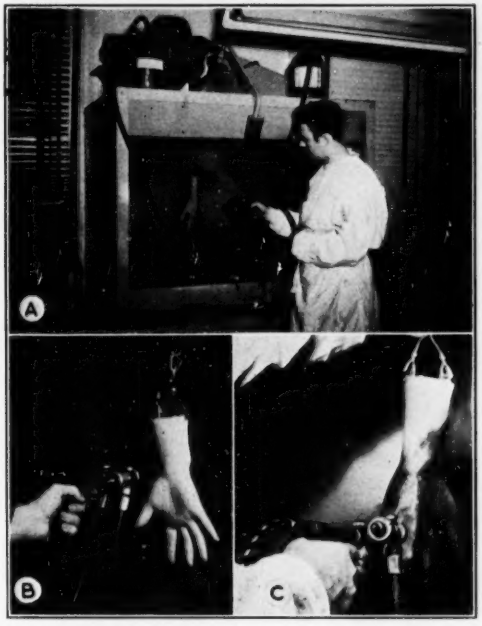



Fig. 1.—*A*, the spray booth for silver spraying. The air supply valve and regulating gage are to the left. On top of the cabinet are bottles of the reducing and silvering agents. These are fed by gravity to the air gun. Such a cabinet must have adequate ventilation. *B*, the dual-nosed air gun. The air is fed through the varicolored hose. The reducing and silvering agents are fed through the black hoses. *C*, as the silver is reduced, it first turns black and then white before a sufficient deposit is built up.

The spraying of the hand pattern is continued until the silver has been precipitated from the ammoniacal silver nitrate solution. It generally requires twenty to thirty minutes to produce a silver film capable of carrying current to receive an electrodeposit of metal. This point may be determined by removing a sample of the deposited mixture and testing for precipitation of silver chloride with a 10 per cent solu-

tion of sodium chloride. The silver deposit may also be tested for its conductivity with an ohmmeter or with a flash light bulb connected in series with two test prods and a dry cell battery.

After the silver spraying, the plastic pattern is rinsed thoroughly in water and allowed to dry. This may be speeded up by subjecting it to an air blast. After drying, the pattern is ready for the electrodeposition of the metal.

Fig. 2.—*A*, electroplating the hand. The rectifier can be seen in the top illustration. The hand is about to be put into the bath. *B*, a detail showing the battery clamp attachment to the silvered hand. The top battery clamp is attached to the cathode rod.

### ELECTROPLATING THE PATTERN OR ELECTROFORMING THE MOLD

Electroplating or electroforming is an established and important subject about which hundreds of articles and books have been written. For the person who wishes to study the subject further, the following books are recommended: "Plating and Finishing Guidebook,"[7]

7. Plating and Finishing Guidebook, 11 West 42nd Street, New York, N. Y., Metal Industry Publishing Company. Published Yearly.

"Principles of Electroplating and Electroforming,"[8] and "Modern Electroplating."[9] Because of the importance of electroforming in preparing metal molds for prosthetic use, the essential facts in relation to the subject are given.

It must be realized that in forming metal molds suitable for making plastic prosthetic hands, the deposit of metal must be thicker than is accomplished in the average electroplating. Most electrodeposits can be figured in millimicrons, while the deposit suited for the metal hand molds should be between 1 and 2 mm. in thickness. Therefore, the pattern must be plated over a comparatively long period at a low voltage. This is necessary because if a high voltage is used, excessive treeing of a crystalline structure takes place. This results in a mold which lacks strength to withstand the rough treatment necessary to remove the pattern and hundreds of succeeding casts from the mold.

*The Electroforming Apparatus.*—In the past most public utilities supplied direct current power. However, today there has been a swing over to alternating current, almost to the point of extinction of the direct current. There are innumerable industrial processes and methods which can be accomplished only by means of a dependable source of direct current power. One of the greatest demands for low voltage direct current is in electrotyping and electroplating. This transition to alternating current has left a gap that had to be filled by suitable rectifying equipment.

There are two types of apparatus on the market suitable for electroplating or electroforming prosthetic hand molds. They are the electric motor generator and the variable metal plate rectifiers. While both are satisfactory, we believe that the variable metal plate rectifier is more serviceable for the following reasons:

1. It has no moving parts.
2. There is no time lag.
3. It is easy to install.
4. It is not necessary to order a unit of higher output than is needed at the time. Extra units can be added to supplement the old.
5. Because the voltage is kept between 2½ and 3 volts, a single unit, having an output of 75 amperes, can be used to electroform from one to five hands at the same time.

These units are capable of producing 6 and 12 volts. However, if higher voltage is used, excessive treeing will occur. Speed of electro-

8. Blum, W., and Hogaboom, G. B.: Principles of Electroplating and Electroforming, New York, McGraw-Hill Book Company, Inc., 1930.

9. Modern Electroplating, New York, The Electrochemical Society, Columbia University, 1942.

plating is governed by a number of factors, such as the voltage employed and the temperature and concentration of the electroplating bath. Because of the low voltage employed, it requires from twenty-four to forty-eight hours to build up a hand mold of sufficient thickness to be serviceable over long periods.

*The Copper Electroforming Bath.*—We find copper to be the metal of choice. There are two main types of solutions suitable for copper plating. They are the cyanide bath and the acid bath. With the present tendency toward substantially heavier copper deposits, the acid copper bath is more important. In spite of the excellence of the cyanide bath for obtaining initial deposits, the relatively dangerous cyanide solution can be eliminated in favor of the comparatively safe acid copper bath.

These solutions must be used in enamelware, glass, crockery or rubber-lined, waterproof steel tanks. We prefer the last.

A satisfactory electroforming solution is as follows:

| | |
|---|---|
| Copper sulfate | 765 Gm. |
| Sulfuric acid | 185 Gm. |
| Water | 4,000 cc. |

This bath is used under the following conditions:

| | |
|---|---|
| Temperature | 23.9 to 48.9 C. (75 to 120 F.) |
| Current density | 15 to 40 amperes, 930.35 cm.$^2$ (1 ft.$^2$) |
| Voltage | 0.75 to 2.0 volts |
| Anodes | Rolled annealed copper |

It is best that air agitation be used. This can be supplied from a small compressor and delivered into the solution through a lead pipe. In such case the bath concentration can be increased and the current density can also be raised, but not beyond 3 volts. If this is increased, unnecessary treeing of the mold and excessive polarization will occur. It is of course best to use an immersion type, electric, temperature-controlled heater in the bath during cold weather.

The following formulas, supplied by the Army Prosthetic Research Laboratory, may also be considered:

Nickel bath for initial covering:

| | |
|---|---|
| $NiSO_4.7H_2O$ | 70 Gm. per liter |
| $NH_4Cl$ | 5.5 Gm. per liter |

$p_H$ 5.8 to 6.0. Operating temperature 34 to 40 C. Current density 0.5 to 0.8 ampere/decimeter,$^2$ with air agitation

Nickel bath for heavy coatings:

| | |
|---|---|
| $NiSO_4.7H_2O$ | 240 Gm. per liter |
| $NiCl_2.6H_2O$ | 45 Gm. per liter |
| $H_3BO_3$ | 30 Gm. per liter |

$p_H$ 4.9 to 5.3. Operating temperature 35 to 40 C. Current density 0.8 to 1.0 ampere/decimeter,$^2$ with air agitation

Copper bath for backing up nickel:

| | |
|---|---|
| $CuSO_4.5H_2O$ | 200 Gm. per liter |
| $H_2SO_4$ | 50 Gm. per liter |
| Glue | 0.01 Gm. per liter |

Room temperature. Current density 1 to 1.5 amperes/decimeter,$^2$ with air agitation.

### METAL SPRAYING

Metal hand molds may be built up entirely over plastic skinform patterns by the metal spraying method alone. For this purpose, tin is the metal of choice, because the temperature of this sprayed metal is sufficiently low to prevent a blistering of the pattern during spraying. Once a deposit of suitable thickness is built up, a metal of higher melting point and tenaciousness, such as zinc or aluminum, may be sprayed over the tin. However, molds of these metals were discarded because they had discoloring effects on the vinyl chloride-acetate plastics used

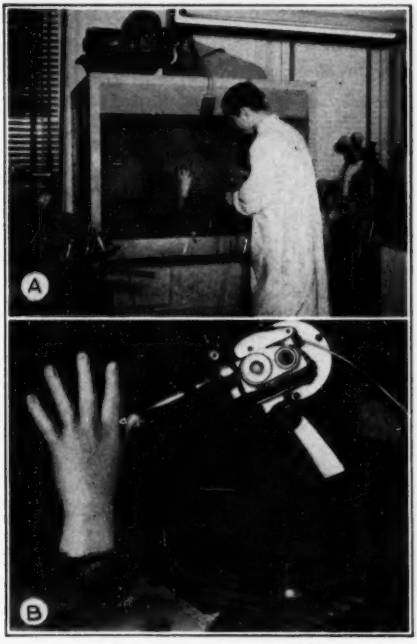



Fig. 3.—*A*, metal spraying may be done in the same spray booth as silver spraying. The metal shown on the spools to the left is fed to the gun, which is held in the operator's hand. The oxygen and acetylene are provided from the tanks to the right. *B*, a close-up showing the molten metal being deposited on the skinform.

in forming the casts. The metal-spraying method produces a thicker deposit in much less time than electroforming. In fact, a mold of sufficient thickness can be built up by spraying in less than half an hour. Furthermore, this method gives sufficient detail so that the resulting hand skinform removed from a sprayed mold cannot be distinguished from the skinform removed from an electroplated mold. Unfortunately,

the sprayed mold is crystalline in structure and will not stand the rough treatment that electroformed molds can be subjected to. We primarily use the metal spraying as an auxiliary method of quickly building up an extra deposit over the electroformed mold. In this way, thick deposits are obtained in less time than would be required by electroforming alone. However, it must be stressed that the electrodeposit must be sufficiently thick before spraying. Otherwise, sections of the two metals will separate one from the other on removal of the pattern.

The equipment for metal spraying may be purchased from any of the firms dealing in this merchandise. It consists mainly of a metal spray gun, compressor (3 horsepower or better) and a power-driven, fan-ventilated spray booth. The metal is supplied to the gun in wire form. The gases for melting the metal are provided from tanks of oxygen and acetylene. These must be rented and are returnable when empty.

### REMOVING THE PATTERN AND MAKING DUPLICATES

Once the metal mold is finished, it becomes necessary to cut off the excess metal cuff, which has been built up by electroforming or metal spraying. This is simply cut away with a hack saw. The mold is then placed in boiling water to melt out the wax, after which it is removed and allowed to cool. After cooling, a long pair of forceps is inserted into the mold, one blade next to the mold and the other blade within the plastic pattern. The mold is then twisted as the forceps are held still. Sometimes it becomes necessary to hold the forceps with a pair of pliers or a vice. On pulling, the plastic hand pattern will either slip from the mold or be torn apart. If it tears apart, this is of little consequence, because the pattern is invariably destroyed in the process of making the metal mold or it is so discolored from the various processes that it is no longer fit for further use. Generally the palm tears from the fingers. The forceps must then be inserted into each finger, one blade next to the mold and the other within the finger, and the remaining part or parts twisted out. The mold can now be washed with water and allowed to dry.

### SEPARATING MEDIUM

Before pouring vinyl chloride-acetate plastic into the hand, it is necessary to treat the mold with one or more separating mediums, so that the resulting cured plastics will readily separate without the excessive pulling necessary in removing the pattern.

The first separating medium we employed was a mixture of:

| | |
|---|---|
| Silicon grease | 50 Gm. |
| Carbon tetrachloride | 960 cc. |

This solution is poured from a bottle into the mold, allowed to stay for a few seconds and then poured back into the bottle. The mold is

then allowed to drain until all dripping ceases. It is then placed in an oven, with the open end up, until all the carbon tetrachloride has evaporated, leaving the thinnest coat of silicon grease on the inner surfaces of the mold. This silicon grease treatment is simple and suffices for making fifty or more plastic skinforms from a single mold before it has to be repeated.

Before the plastic is poured into the silicon grease–treated mold, it can be further treated with another silicon separating medium. This is Dow Corning Corporation's[10] Mold Release Fluid Number 35, which is an emulsion of silicon grease and therefore soluble in water. This is prepared in the following proportions:

| | |
|---|---|
| D. C. Mold Release Fluid No. 35 | 250 cc. |
| Water | 750 cc. |

This mixture is poured from a bottle into the metal mold, allowed to remain for a few seconds and then poured back into the bottle. The mold is then hung in the oven with the open end down for draining. After drops have ceased to appear, the mold is inverted and complete drying is allowed to take place.

After complete drying, the mold is ready to receive the plastic. The first pouring of plastic should be done while the mold is cold. Where hot molds are concerned, it must be realized that the higher the temperature of the mold, the thicker will become the deposit of plastic. We find it better and advantageous to pour the plastic two or more times into the heated mold before a hand of desired thickness is obtained. Each time the mold is allowed to drain back into the original container until dripping ceases. It is then heated again for from four to six minutes in an oven of 100 C. and the pouring and draining repeated. After the final draining, the mold is placed back into an oven at 135 C. until completely cured. This takes place when all parts of the plastic have reached 135 C. and requires about ten minutes.

Some workers prefer to effect the final cure in glycerin. This is accomplished in the following manner. After the mold has been drained of plastic for the final time, it is placed in the oven for sufficient time to set the plastic. This can be determined by the fact that the inner surfaces of the cast will have lost their gloss and will no longer be sticky to touch. The mold is then removed to the hot glycerin bath, which should not exceed 150 C. Here it may remain for five minutes. The glycerin is drained from the mold, and the hot mold is placed in cold water. After complete cooling, the skinform hand can be removed from the mold without difficulty as a result of using the silicon separating medium. It is then ready for making a prosthesis for a full or partial hand.

10. Midland, Mich.

THE PARTIAL HAND PROSTHESIS

A plaster of paris or dental stone duplicate or cast is first taken of the patient's injured member. The mold may be of either agar composition or gypsum cement (plaster of paris–water mixture). A vent must be made through the wrist, to be used later as an air escape. This is important because, in a process to be explained later, air must pass through this vent during the expansion of foam plastic.

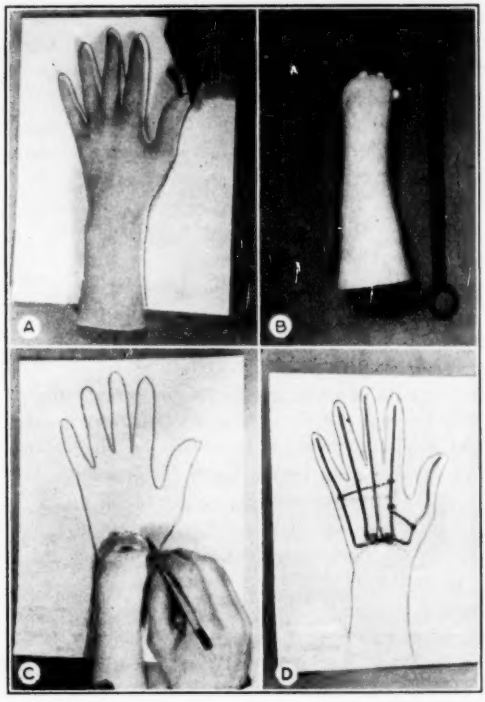



Fig. 4.—*A*, making the partial hand prosthesis. The skin form suited to the patient is chosen and its outline is traced on a piece of paper. *B*, a plaster cast of the affected or injured member with the vent former. *C*, an outline of the affected member is traced in the proper position on the paper. *D*, the wire finger armature is constructed to fit the proper space.

This vent can be created by inserting a vent former. Such an instrument may be made of stiff, 10 gage wire covered with rubber tubing. The rubber covering of the vent former is painted with a vaselin–mineral oil separator and the protruding point of the wire stuck into the center of the hand portion of the mold before it is filled with

gypsum cement. Its central position is maintained in the arm until the gypsum has set sufficiently to hold it. When the cast is completely set, the mold is removed and the vent former withdrawn. The cast is then painted with a green soap separator and set aside to dry.

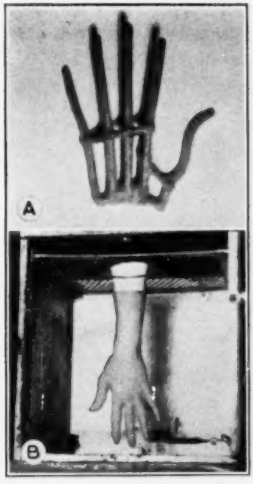



Fig. 5.—*A*, the wire armature after dipping in plastic. *B*, the wire armature is put in place in the skinform. The foam is added, and the plaster cast of the affected member is inserted. The composite casts are placed in the oven for expanding the foam.

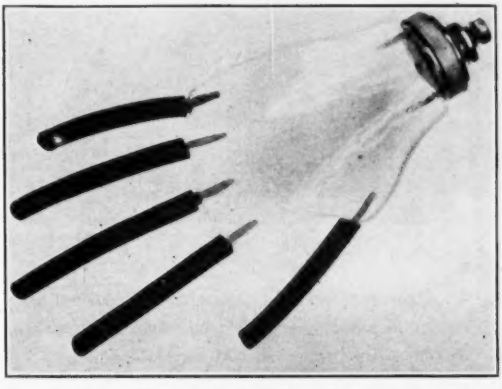


Fig. 6.—*A*, a wire rubber methyl methacrylate armature, devised by the Prosthetic Laboratory of the Veterans Administration for using in the skinform for total hand prostheses. The foam is applied between the armature and the skinform.

The cosmetic glove or skinform selected for its similarity in size and character to the patient's unaffected hand is laid on a piece of white paper and carefully traced in pencil. Next the patient's injured hand or the plaster cast is placed on this tracing, and the line indicating the extent of his loss is traced. With the area to be filled or replaced reduced to a line drawing, the next step in making a necessary wire skeletal device becomes much easier. This wire frame or skeletal device is made to provide the missing fingers with the necessary

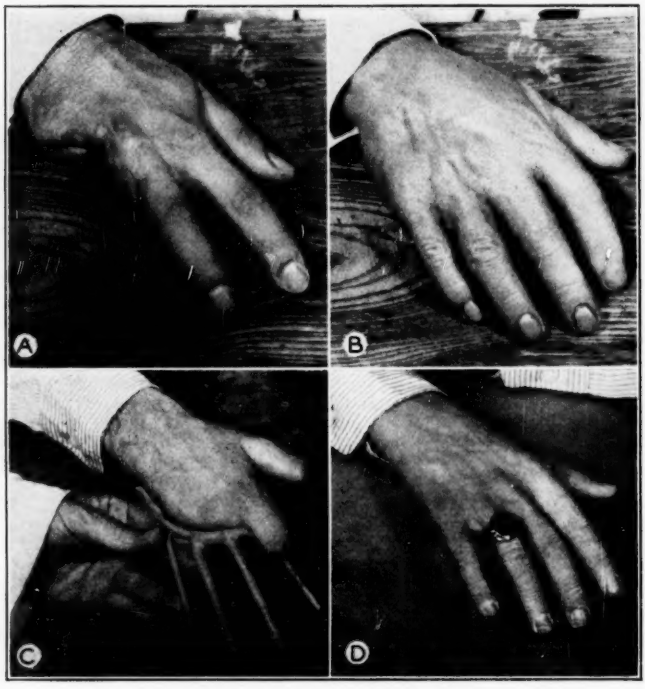



Fig. 7.—*A*, an affected member. *B*, the completed plastic prosthesis on the patient. *C*, an affected member, showing the plastic-covered armature in place. *D*, the completed plastic prosthesis on the patient.

rigidity and to allow for flexibility, so that the patient may bend the fingers with the good hand to any desired position, permitting gripping and holding. This wire frame should extend as far as possible into the palmer area to insure a proper change of plane at the knuckles when the hand is cupped or made into a fist. The device is made of 8 gage copper wire, flattened and soldered with acid core solder if

more than two fingers are to be replaced. The flattening is accomplished by using an anvil and ball peen hammer. The portions to be soldered are then sanded and bound with fine copper wire. After completion, the soldered device is next heated over a gas stove flame and dipped while hot in a vinyl plastic. Here it is allowed to remain for two

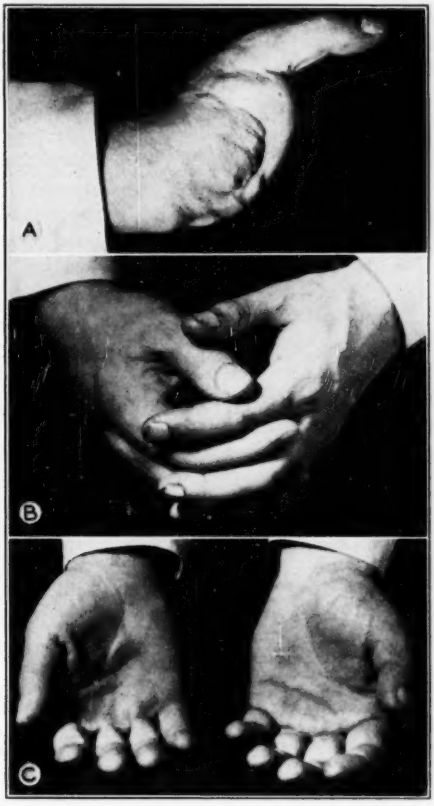



Fig. 8.—*A*, the affected member. *B*, the natural hand being clasped with the prosthesis. *C*, the inner surfaces of the prosthetic and the natural hand for comparison.

minutes to build up an insulating coat or deposit. On draining, it is cured for half an hour at 100 C. and is ready for a trial fit.

The plastic-covered metal skeletal device should be trial fitted in the skinform with the cast of the patient's hand in place. The skeletal fingers should extend to the tips of the glove to insure their bending to

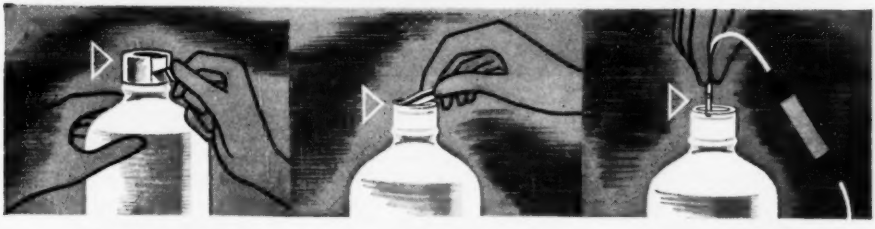
the last joint. However, if any finger of the skeletal device is long enough to stretch the skinform, the offending tip should be pared down with a pair of pliers or scissors or a sharp knife until no tension is apparent. This is to prevent possible breaking as a result of stress during curing.

For filling the area between the hand skinform and the plastic-covered metal skeletal device, we have found foam plastic satisfactory. Before the foam may be used, however, it is important that all curing glycerin be removed from the inside of the skinform to insure the foam adhering to the inside surfaces. In addition to thorough washing, a 2 to 6 per cent dilution of amyl alcohol or cyclohexanone may be added to the foam plastic. For best results the foam plastic should be mixed with from 1 to 2 per cent of water just prior to use. The fingers of the skinform corresponding to the missing digits of the cast of the patient's hand are filled with the liquid foam plastic. The wire frame is then inserted into the skinform and rechecked to insure that it extends to the finger tips. This is done to insure automanipulation of the finished prosthesis to the distal phalanges. Next the prepared plaster cast of the patient's partial hand is inserted in the wrist opening. These are hung in the oven by a wire attached to the wrist of the cast. The temperature of the oven should be started at 70 C. and gradually increased to 100 C. This temperature should be maintained for three quarters of an hour before the hand is removed. The reason for the low starting temperature is to allow the foam time to expand fully before setting. If the heat is regulated correctly, the volume of the foam will be doubled on curing. On removal from the oven, the filled skinform is allowed to cool thoroughly before the cast is removed. When this has been done, the prosthesis is ready for coloring and fitting on the patient. Coloring has been explained in detail in the book "Facial and Body Prosthesis." [11]

11. Clarke, C. D.: Facial and Body Prosthesis. St. Louis, C. V. Mosby Company, 1945.

# 3 SAFE, SIMPLE STEPS

## prepare Cutter Saftiflask for use



**1 Remove outer Saftiseal by pulling raised tear tab.**

Cutter's large-sized tab permits easy removal of the tamper-proof outer metal Saftiseal. Cap is then ready for quick removal in one simple motion.

**2 Lift vacuum-sealed rubber liner from lip and stopper.**

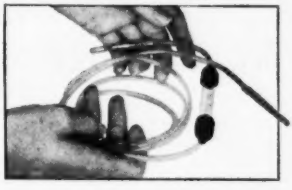
Cutter's rubber liner protects sterility around the lip and across the stopper. When liner is lifted, the safety signal of protective vacuum is clearly audible.

**3 Insert Expendable I. V. Set into outlet hole of Saftiflask stopper.**

Cutter's specially designed ring of live rubber within the stopper allows easy insertion of connecting tube and secures the tube firmly in place.

**Expendable, Sterile, Pyrogen-free, Ready-to-use I. V. Set.** Combine this ready-to-use disposable set with sterile, pyrogen-free Cutter Solutions in Saftiflasks for a streamlined, functional I. V. infusion set-up.

In addition to the plastic I. V. Set shown (also available with rubber tubing), Cutter's complete line of expendable equipment includes Hypodermoclysis and Y-tube sets, Blood and Plasma infusion sets, and Donor set.



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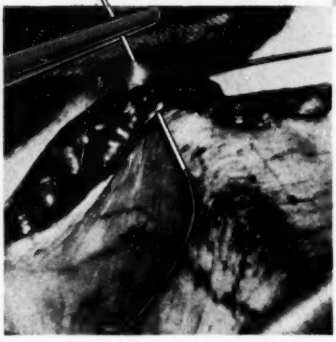

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